FEB 12 1917
UNIV. OF MICH.
LIBRARY

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

Vol. XXVIII.—No. 312.] BALTIMORE, FEBRUARY, 1917. [Price, 25 Cents

CONTENTS.

	PAGE
Regeneration in Peripheral Nerves. An Experimental Study. (Illustrated.) By Edwin G. Kirk, M. D., and Dean D. Lewis, M. D.	71
The Significance of Xanthochromia of the Cerebrospinal Fluid. By T. P. Sprunt and J. E. Walker	80
Multiple Spontaneous Intracerebral Hemorrhages. A Contribution to the Pathology of Apoplexy. (Illustrated.) By Phyllis Greenacre	86
Titles of Papers Appearing During the Year, Elsewhere than in the Bulletin, by Present and Former Members of the Hospital and Medical School Staff	89
Proceedings of Societies. The Johns Hopkins Hospital Medical Society. Exhibition of Cases: Cases 1, 2 and 3 [Dr. Dandy];—Exhibition of a Case of Gigantism in a Girl 12 Years of Age [Dr. G. J. Heuer];—Action of Opium Alkaloids on the Ducts of the Testis [Dr. David I. Macht];—Studies on the Physiology of Thyroid Secretion. (Abstract.) [Robert L. Levy, M. D.];—Some Results of Plastic Surgery [Dr. J. S. Davis].	96
Books Received	98

REGENERATION IN PERIPHERAL NERVES.*
AN EXPERIMENTAL STUDY.

By Edwin G. Kirk, M. D., and Dean D. Lewis, M. D., Chicago.

(From the Morris Institute of Medical Research of Michael Reese Hospital.)

In a previous communication[1] it was shown that nerve defects may be bridged successfully by tubulizing with an autotransplant of fascia. Although devised primarily with reference to practical surgical use, it soon became apparent that the method afforded unusual opportunities for a study of the histology of nerve regeneration following mechanical trauma. Fig. 1 (*A* and *B*) illustrates the technique employed, which is described in detail in the article referred to. The defect is produced by excising a segment, varying in length from 1 to 3 cm., the nerve being cut squarely across with a sharp knife. Fascia lata from the same animal is used to construct the tube, since by using an autotransplant fibroblastic reaction and subsequent cicatrisation are avoided. Thus regeneration following trauma may be studied without interference from various external factors and in particular the ingrowth of cicatricial tissue between the ends. Most important of all, the comparative behavior of proximal and distal stumps is more easily determined than when the ends are approximated.

* Read before The Johns Hopkins Hospital Medical Society, April 3, 1916.

[1] Fascial Tubulization in Repair of Nerve Defects. Sect. Surgery, A. Med. Assoc., San Francisco, June, 1915; J. A. M. A. 1915, LXV, 486-491.

Material and Technique.

The material used in the present report includes 41 sciatic nerves of adult dogs, 21 of which are in complete serial section. The animals were killed at periods varying from one day to 36 weeks after operation. In general, four methods of histological preparation have been employed: (a) Fixation in Bensley's fluid (Müller's fluid saturated with mercuric bichloride and with 10 per cent of formalin added just before use) and staining in Mallory's phosphotungstic acid hematoxylin. Myelin sheaths are stained an intense blue; the axis-cylinders are unstained or are light blue; the chromatic elements of neurilemmal and other nuclei blue; and connective tissue red. (b) Cajal-Ranson silver impregnation—following Held's pyridin technique. The non-medullated fibers are an intense black, the axis-cylinders of medullated fibers a yellow brown, and the general background of tissues a light yellow. (c) Hematoxylin and eosin—especially in the study of protoplasmic bands. (d) Often the silver preparations were counterstained with safranin.

The Early Stages.

An exudate of serum into the empty fascial tube begins on the first day. At the end of 72 hours the tube is partially filled with serum containing a few mononuclear migratory cells. If hemostasis has been adequate, there will be prac-

tically no erythrocytes. By the fifth day the portions of the tube nearest the two nerve stumps are filled with a soft grayish-white pulpy material, resembling in appearance soft brain matter. The exudate comes from the nerve ends, the fascia showing no reaction. Microscopically this pulpy material is finely granular and homogeneous—evidently coagulated lymph. Sometimes the middle portion of the tube, the part most remote from the divided nerve ends, is still empty on the fourth or fifth day.

Early Changes in Axis-Cylinders and Myelin Sheaths.

On the basis of his own observations and those of others, Ranson (1912) comes to certain conclusions which we have been able to confirm. We shall, therefore, give them only a brief consideration, referring the reader to his work for details. In both stumps there occur during the first two to three days abortive regenerative changes, manifested in the outgrowth of fine terminal and lateral neurofibrillar rami from non-medullated as well as from medullated axis-cylinders, in the dissociation of the axis-cylinders into bundles of fine neurofibrillæ, and in the development of delicate plexuses of such fibrillæ beneath the neurilemmal sheaths. These abortive fibers appear in the proximal and also in the distal stumps, but only in the immediate vicinity of the section (a few tenths of a millimeter). They degenerate completely in from three to eight days. Ranson has demonstrated the temporary nature of these phenomena in the distal stump, where they have often been mistaken for definitive regeneration. Certain degenerative phenomena also develop early. In both stumps the axis-cylinders and myelin sheaths of medullated axones degenerate for a distance of about 0.3 mm. (second to third day). The non-medullated fibers of the central stump also exhibit a slower, ascending degeneration (third to eighth day), which extends upward for about 1 cm. The Wallerian degeneration, occurring later, is somewhat slower, and is observed in the whole distal segment—the axis-cylinders becoming swollen and fragmented (second to fourth day), and the degeneration of the myelin sheaths quickly following (fourth day). Definite regenerative changes occur in the central stump only. By the eighth day the medullated fibers have given off numerous lateral rami higher up (5 mm. and less from section), these growing down as subneurilemmal fibers within the old sheaths. The non-medullated fibers also dissociate into bundles of neurofibrillæ, which grown down in the sheath (by the fourteenth day). At the end of one month all the medullated and non-medullated fibers in the last 5 mm. of the proximal stump have been converted into bundles of non-medullated fibers, each bundle containing from 20 to 60 fibrillæ or more. These are much more numerous than in the normal nerve. Ranson suggests a teleological explanation of this hyperregeneration—with special reference to the number of fibers which must later go astray in the scar.

Changes in Neurilemmal Sheaths.

As is well known, the adult neurilemmal sheath (Schwann) of peripheral nerves is a fine, thin, structureless membrane almost invisible and provided with a very few, fusiform nuclei—one to each node of Ranvier, the length of the latter varying from 80 to 900 μ. The nuclei are surrounded by a very small quantity of cytoplasm. Mitoses are not present in the resting stage. Fig. 2 illustrates the maximal number and the appearance of neurilemmal nuclei in an adult peripheral nerve. It is rarely possible to find so many in one field. Note that the cytoplasm is practically invisible.

We believe that the phenomenon now to be described is of the greatest importance in the regeneration, or attempted regeneration, of nerves. We refer to the very early reaction of the neurilemmal sheaths adjacent to the point of section of both proximal and distal stumps. This is a hyperplastic reaction, the adult (resting) neurilemmal sheath, with its nuclei, reverting to the active or embryonic type. The first indications of this activity are seen in a slight increase in the amount of granular cytoplasm surrounding the nuclei, or rather a becoming visible of the previously invisible cytoplasm. We have seen this first between the twenty-fourth and thirty-sixth hours in the portions of the neurilemmal sheaths closest to the level of section. This earliest change is demonstrable only with difficulty. The cytoplasm surrounding these nuclei increases rapidly in amount the next two days, and the nuclei increase rapidly in number by mitosis, so that between the fourth and sixth days the protoplasmic bands (the primitive *Bandfasern* of earlier authors) become well developed (Fig. 3). These are narrow strands or bands of cytoplasm containing the now hyperchromatic and active neurilemmal nuclei. By the fifth or sixth day numerous protoplasmic bands have already invaded the serum of the fascial tube, and from that time on they proliferate continuously down the tube. Fig. 4 shows the bands running down into the serum from the proximal stump. At their point of origin—namely, in the last .2 or .3 mm. of the proximal stump, they constitute thickened bands of cytoplasm within the neurilemmal sheaths. Their relation to the resting neurilemmal sheath is shown diagrammatically in Fig. 1, *c*, in which (*a*) represents the neurilemmal nucleus, (*b*) the thickened cytoplasm, constituting, as seen in longitudinal preparation, the *Bandfaser* or protoplasmic band, and (*c*) the non-hypertrophied parts of the sheath, the whole presenting the appearance of a seal-ring.

Thus the position of the nucleus determines the point of development of the band within the sheath. As soon as the band leaves the nerve stump and goes down into the serum, it appears as a solid, somewhat flattened, strand of cytoplasm, not as a tube; for the thin portion (*c*) either atrophies, or more probably collapses, and fuses with the protoplasmic strand, obliterating the lumen of the sheath.

In preparations such as are represented in Microphotograph 4, it is important to observe that these protoplasmic bands are traceable in absolute continuity from the terminal portion of the stump down into the serum of the tube. The transplanted fascial tube at this, as at all levels, displays no fibroblastic reaction.

Fig. 3 shows an area ($\times 1000$) from the proximal stump 2 mm. above the plane of section on the sixth day. Note be-

tween the large medullated fibers, the slender protoplasmic bands with numerous neurilemmal nuclei, some having just divided—all rich in chromatic material.

Fig. 5 shows in detail an area from the same nerve at the very tip of the proximal stump. Note the swollen degenerated medullated fibers and sheaths, and between them the protoplasmic bands with their neurilemmal nuclei.

Precisely the same phenomenon occurs in the distal stump. Fig. 6 is a low-power picture (×335) of the proximal end of the distal stump of the nerve represented in Figs. 3 and 5. Note the swollen degenerated medullated fibers and sheaths (*a*) and between them the hyperplastic neurilemmal bands (*b*), the latter also growing up into the serum of the tube at *c*.

Fig. 8 shows an area of the same distal stump just below the plane of section. Note here again the large swollen fragments of medullated axis-cylinders and their myelin sheaths, the material of the latter clumped as "ovoids," in the midst of which are the semi-digested remnants of the axis-cylinders. Between them are the hyperplastic neurilemmal nuclei and their bands of protoplasm (*a*). The latter are not quite as numerous or as well developed as in the proximal stump. Fig. 7 shows the very tip of this same (distal) stump, illustrating the additional feature of the growth of bands into the serum at *a*. Here also may be seen fragments of degenerated axis-cylinders surrounded by the "ovoids" of myelin (*b*). Although this outgrowth of neurilemmal protoplasmic bands occurs at both the proximal and distal stumps and is of a similar nature in each, it is much more active at the proximal end. Thus the bands rapidly progress into the serum from the proximal end, and much less rapidly from the distal, so that they meet at a point much nearer the distal than the proximal stump. The approximate rapidity of growth is indicated by the fact that, after removal of a segment 12 mm. long (Nerve 79), the protoplasmic bands have completely bridged the tube of serum by the sixth day, being very numerous near the proximal stump (Figs. 3 and 5), much less numerous near the distal stump (Figs. 6, 7 and 8) and least numerous at a point about 10 mm. from the end of the proximal and 2 mm. from the end of the distal stump (Fig. 9). This last level represents the meeting point of the two sets of protoplasmic bands. All these phenomena occur earliest in the last millimeter of the proximal and the first millimeter of the distal stump. On the sixth day the process is most marked, that is, the protoplasmic bands are largest and most numerous, and their nuclei most hyperplastic, at their very tips. At a distance of 1 mm. from the tips the process is decidedly less active, that is, the nuclei, although many times more numerous than in the normal nerve, are yet strikingly less so than at the very tip, and the protoplasmic bands are not so long or numerous. At a distance of 2 mm. there is still a decided increase in the number of nuclei and a considerable increase in the cytoplasm surrounding them as compared with the normal resting nerve, but no distinct band-formation. This applies to both stumps. In the lower stretches of the distal stump, more than 2 mm. from the plane of section, the hyperplasia of nuclei is not very evident until the fourth day, and the protoplasmic bands are not well formed until the ninth day and later. It will be noted below, in the review of the literature on neurilemmal hyperplasia, that we describe this phenomenon as developing at a time considerably earlier than that noted by various other investigators. Thus we find that well-formed protoplasmic bands have invaded the exudate in the tube as early as the fourth or sixth day, whereas others describe them as appearing first about the eighteenth or twenty-first day. The explanation of this apparent discrepancy has already been hinted at. The process of hyperplasia is essentially of the nature described throughout the whole of the distal and the lower end of the proximal segments, but certain factors, doubtless largely the mechanical trauma, greatly accelerate the process in the last millimeter of the proximal and in the first millimeter of the distal stump. In the immediate vicinity of the severe nerve injury, associated with a break of continuity, there occurs a special acceleration of the process of protoplasmic band-formation. It is obvious, from the facts recorded above, that this may be regarded as nature's effort for insuring a pathway for the regenerating axis-cylinders. In ordinary nerve repair this regenerative process is often interfered with by the ingrowth of extraneous cicatricial tissue. All former descriptions of the neurilemmal hyperplasia and formation of protoplasmic bands are based on the process as it occurs at a distance of a millimeter or more from the level of section. Doubtless, this is due to the fact that this outgrowth of neurilemmal bands was considered to be atypical, or that with the ordinary methods of approximation the cicatricial reaction obscured this feature of the process. No one to our knowledge has observed this accelerated neurilemmal hyperplasia occurring at the end of the segments. Ingebrigtsen's speculation as to the difficulty of finding such bands in the scar is suggestive in this connection. Of course the accelerated *degenerative* phenomena at this location have often been noted. Howell and Huber (1892) observed that, in the immediate neighborhood of the wound, degenerative changes of traumatic origin undoubtedly occur before they appear in the rest of the nerve. Ranson also mentions the rapid traumatic degeneration in the immediate vicinity of the plane of section.

Morphology of the Bands.

The protoplasmic bands, as they grow down into the serum, anastomose frequently. This is best demonstrated by a serial study of cross-sections (of which Fig. 13 shows one); but it is also seen in the longitudinal preparations (Figs. 9, 10, 11). The anastomoses are much better demonstrated on the corresponding specimens by focussing in various planes. In Fig. 9 the most conspicuous elongated band (*b*) is seen branching just as it leaves the plane of the section. Sometimes, however, the bands run for about 100-200 μ without anastomosing (Fig. 12). These bands are often very difficult of demonstration, as their cytoplasm does not stain well. Sometimes they are rendered visible by the silver technique, taking a faint yellow color. In general, the best preparations were obtained with hematoxylin and eosin, or with safranin.

The recent observations of Ingebrigtsen (February, 1916) are of interest in this connection. On incubation of peripheral nerves in plasma, a growth of the sheath of Schwann occurs, provided the axis-cylinders and myelin have undergone Wallerian degeneration previous to the implantation. There is a striking resemblance between the neurilemmal bands as we find them in the serum of the fascial tube, and the ones pictured by Ingebrigtsen.[2] After three to four days' incubation in plasma, there grow out from the cut ends of the nerve fibers numerous thin filaments of protoplasm, highly refractile and slightly granular. At first they are tapering, and end in a point which shows amœboid movements, by means of which they emerge into the plasma. They soon become more or less cylindrical, and branch and anastomose. The average width is 6 to 8 μ. The bands contain nuclei of an elongated ovoid or fusiform shape. Inasmuch as the nuclei are slightly greater in diameter than the protoplasmic band, the latter shows a slight expansion at the site of each nucleus. After six days' incubation the bands anastomose very freely. As in our preparations, there are often stretches of such bands measuring 200 μ or more in length, devoid of nuclei (Ingebrigtsen's Fig. 4). In the summary Ingebrigtsen speculates as follows: "Is this an indication that such an outgrowth occurs from the cut end of a degenerating nerve in the organism, and plays some part in the processes of union and regeneration? I have never seen it, and I am not aware that it has been noticed by other observers. But it is probable that such a growth from the cells of Schwann of the peripheral part of a divided nerve extends into the scar tissue forming part of it. That structures of this kind have not yet been detected in the organism does not prove their non-existence. They stain faintly, and curving and bending through the scar tissue it may be difficult to bring out their true form." In a critique of neurotropism he says: "An anatomical conception of the centrifugal orientation, based upon my experiments, seems more satisfactory, assuming that the protoplasmic syncytium of Schwann growing out from the peripheral part of a divided nerve, branching into the scar, may receive the axis-cylinders coming from the central part, and serve as a guidance for them into the peripheral segment."

We had already (Kirk and Lewis, December, 1915, and January, 1916) answered these questions affirmatively.

Stellate and branching connective-tissue cells are also found in the serum of the tube near the nerve stumps. They are derivatives of the endoneural connective tissue. Ingebrigtsen observed these along with the neurilemmal bands in plasma cultures. Lymphocytic migratory cells also find their way into the serum of the tube (see Fig. 9).

Nageotte (1911) has shown the adult (resting) neurilemmal sheath to be a syncytium. Ingebrigtsen's observation (1916) that the test-tube growths of neurilemmal bands show frequent anastomoses after a few days' incubation, while the axis-cylinders never do, is of significance in this connection. This feature of the structure is brought out in relief in the hyperplasia, even in those parts removed from the sectioned ends, the protoplasm of adjacent sheaths being continuous. We have already referred to the frequent anastomoses in the bands as they grow into the serum. Thus it seems to us a misconception to speak of the protoplasmic bands as appearing on the fourteenth day or on the eighteenth day by fusion of the previously isolated masses of cytoplasm. From their inception they form a continuous plexus that simply becomes more protoplasmic as hyperplasia advances. This is the first time, so far as we are aware, that the tubulization technique with separation of the two nerve ends has been applied to the study of the behavior of the protoplasmic bands. It has, of course, long been recognized that at some time (two to three weeks) after the initial trauma, the hyperplasia of neurilemmal nuclei and associated cytoplasm gives rise to the formation of the so-called "primitive Bandfasern," both in proximal and distal segments.

Büngner's observations (1891) are of unusual interest. Unfortunately, owing to the use of the inferior technique of that day, he erroneously interpreted certain longitudinal striations appearing in these bands in the distal segment as representing new axis-cylinders developing by peripheral regeneration, an error hardly possible with the use of the silver technique (see Ranson for a critique of Büngner's work). Büngner's descriptions and figures of the protoplasmic bands are very accurate. On the third day after crushing or cutting of the nerve the nuclei of Schwann in both proximal and distal stumps become hyperplastic and divide by karyokinesis. Cytoplasm accumulates about them on the inner surface of the thin sheath, and that surrounding the individual nuclei rapidly forms bands by fusion. Nuclear activity is at its height between the fifth and eighth days. Cross-sections of these bands often show (*e. g.*, his Fig. 10) the typical seal-ring appearance mentioned above. Myelin fragments are, as usual, often present in the protoplasm of the bands.

Howell and Huber (1892) describe hyperplasia and proliferation of the neurilemmal nuclei and associated cytoplasm on the seventh day, at points some distance distal to the level of the section. On the twenty-first day they find well-developed "embryonic nerve fibers" (protoplasmic bands). These develop in the central and peripheral segments and arise from the neurilemmal cytoplasm. They make the important observation that the regenerating axis-cylinder is found in the embryonic nerve fibers of the proximal stump. They also find them within the same bands of the distal stump. They speculate as follows: "How is the connection between the two made? It is practically an impossible thing to witness the making of this connection, but we are strongly convinced that it takes place in the cicatricial tissue, and chiefly from the downgrowth of embryonic fibers from the central end." Speaking of the intervening scar they say: "It forms a tissue into which the actively growing embryonic fibers from central and peripheral ends penetrate, and finally meet and unite" (p. 384). They made the observation (confirmed by Ranson in 1912, and by us) that, if the cicatrix prevents union of the two ends, the protoplasmic bands still form in the distal

[2] Compare, for example, Ingebrigtsen's Fig. 3, plate 34, with our figures.

stump, this being then the sole manifestation of peripheral regeneration.

Our present work not only confirms Howell and Huber's as to the absolutely autochthonous formation of the bands in the proximal and distal stumps, but also shows that, before any axis-cylinders grow from proximal into distal segment, the bands must grow across the gap (or cicatrix), and prepare the way. (See section below on "Neurilemmal bands as pathways.")

Huber (1892) studied the behavior of neurilemmal nuclei after section of nerves in rabbits. At two days the nuclei are enlarged, ovoid, hyperchromatic and surrounded by an increased amount of cytoplasm. Mitoses are present at the end of the third day. The distribution of the dividing nuclei throughout the Ranvier segment is believed to be due to an active motility of nucleus and adjacent cytoplasm.

Huber (1895) describes in implanted nerve segments a similar hyperplasia of neurilemmal nuclei, but not so marked as in the distal segments. After from six to nine days the neurilemmal sheaths are described as much collapsed, containing a little cytoplasm and a few nuclei.

Ballance and Stewart (1901) describe and figure a marked proliferation of neurilemmal cells beginning on the second day (their Figs. 1 and 2, Pl. 15). They lay no emphasis on any functional activity of these cells until later stages are reached. Ranson (1912) finds typical protoplasmic bands in the distal segment on the nineteenth day, developing from medullated and non-medullated fibers.

The Neurilemmal Bands as Pathways for Axis-Cylinders.

Our observations prove conclusively that the protoplasmic bands constitute conduits, in the substance of which the non-medullated fibers of regeneration from the proximal stump rapidly grow down (Figs. 10, 11, 12 and 13).

On the sixth day such axis-cylinders are already found in many bands at a distance of 1 mm. from the extreme end of the proximal stump. Sometimes the fiber is well embedded in the cytoplasm, sometimes it lies very near the surface. We have best demonstrated these relations by impregnating with silver, and then rapidly counterstaining with safranin. The bands grow down first, and the nerve-fibers follow along them. This is determined in both longitudinal and cross-sections. In the former, many bands will be seen which contain no fibers. At the six-day stage the bands are found to contain fibers only in the first millimeter from the central end, although the bands have bridged a gap of 12 mm. The down-growing axis-cylinders will not completely bridge this same gap and reach the distal segment in less than three weeks. After four weeks numerous fibers have passed through a gap of about this extent and entered the distal stump (Fig. 20). In the serial transverse sections, except in stages so far advanced that neurotisation is complete across the gap, one can compare sections at the upper part of the tube, in which many or most of the bands contain axis-cylinders, with those from lower levels in which the bands are devoid of them. Photograph 13 was taken at such a level that some of the bands show an invasion by axis-cylinders and some have none. The axis-cylinders are stained an intense black by the silver. Note the numerous neurilemmal nuclei as seen in cross-section. The bands first enter the serum as separate strands, but a little later anastomose to form a very complete rete. Thus it comes about that the bundles of regeneration from various axones often partially interlace (Fig. 19). Ranson (1912) also has described this condition (his Fig. 27).[2]

We do not wish to imply that the axis-cylinders always and necessarily track along the protoplasmic bands; for it is definitely known that, under special and unusual conditions, such is not the case. Ingebrigtsen (1913) cultivated cerebellar tissue *in vitro* (plasma media), and obtained growths of axis-cylinders. This result was confirmed later (Ingebrigtsen, 1913) by Cajal's silver method. They grow out into the plasma unaccompanied by structures of any kind, and do not anastomose. Here the advancing axis-cylinders were supported by a surface. The same experiments also showed outgrowth of neuroglia fibers as an anastomosing rete. Clark (1914) produced experimental polyneuritis (beri-beri) in fowls by feeding polished rice. Myelin sheaths and axis-cylinders of peripheral nerves were brought to any desired stage of degeneration. All traumatic and inflammatory effects, such as are produced by sectioning or otherwise interrupting the continuity of fibers, were thus avoided. Under proper diet, regeneration of axis-cylinders and myelin sheaths, the former always from the central end toward the periphery, could be induced. Only in the most advanced and prolonged degenerative changes of cylinders and myelin sheaths did he ever find multiplication of neurilemmal nuclei. Here again is an example of the down-growth of axis-cylinders without the aid of tracks in the shape of protoplasmic bands. In this case it is obvious that there is a tubule preformed for the conduction of each regenerating fiber. But while under such exceptional conditions nerve fibers may grow down independently of the bands, we are convinced from our observations that in regeneration following trauma—and such embraces practically all cases in which surgical intervention is indicated—a pathway across the cicatrix, or from proximal to distal stump in case of apposition of the ends, is prepared only by these bands. When they are deflected as by the cicatrix, the axis-cylinders following them are likewise deflected (Fig. 10).

We have already mentioned that Howell and Huber (1892) describe and figure the regenerating axis-cylinders as being situated within the embryonic nerve fibers of both proximal and distal stumps. Huber (1895) verifies the down-growth of axis-cylinders into the old sheath of Schwann, filled with cytoplasm, in the lower part of the central stump; also within and between the old sheaths in implanted segments; and in the same localities in the peripheral stump.

Harrison (1908) cut nerves in the tail of frog larvæ and found that the proximal and distal stumps of many fibers were united by strands of protoplasm on the second day. When this

[2] Nageotte (1911) has shown the protoplasm of the neurilemmal sheath in the resting condition to constitute a syncytium.

occurred, degenerative changes in the peripheral segment were inhibited. These results are not surprising, in view of the great regulative power shown by tissues of lower vertebrates, and especially of larvæ. Ranson (1912) particularly emphasizes the use of protoplasmic bands of the distal segment as pathways for the invading axones. He finds the bands well developed on the nineteenth day, and new non-medullated fibers from the proximal stump already running in their proximal portion. *These axis-cylinders always run down in the bands, never between them.* Several axis-cylinders often lie within one band (his Fig. 29). Dustin (1913) believes that nerves heal by a special type of cicatrix formation. In the primary connective-tissue scar are organized paths of least resistance (Leitbahnen), through which the nerve fibers pass. This specific cicatricial tissue is found only between nerve fibers, and is derived from the connective-tissue cells of the nervous system. It rapidly forms a "porous callus," and unites the stumps provisionally but exactly. Nageotte (1915) discusses "the process of cicatrisation in nerves" in a brief report, based on the study of two (2) nerves at the fourth week of regeneration. The nerves were sectioned; one was tubulized with a vein, the gap measuring 1.7 cm.; the other was bridged with silk, the defect measuring 1.4 cm. Each animal was killed after one month, and the nerve fixed in formalin and stained in iron hematoxylin and Van Gieson. He concludes that the young axis-cylinders grow down only in a syncytial network derived from the sheath of Schwann. He assumes the sheath to be of ectodermal origin, and maintains that the axis-cylinders never grow naked into the mesenchyme, but always surrounded by this ectodermal sheath, several axis-cylinders often within one sheath. The sheaths regenerate from both the proximal and from the distal stumps. He believes that the axis-cylinders cannot exist apart from the ectodermal sheath. It is difficult to conceive how Nageotte has been able to arrive at these elaborate deductions from two specimens each at the fourth week. We believe, however, that he has seen at a later stage the same phenomenon which we have seen in a series ranging from one day to 36 weeks. We cannot concede that the axis-cylinders and neurilemmal bands of the proximal stump grow down at the same time. The latter certainly precede the former.

Ranson (1912) and others have already abundantly demonstrated the origin of the new axis-cylinders from the stumps of non-medullated and medullated fibers. As they have shown, there is an immense over-production of fibers. This is illustrated repeatedly in our series. Fig. 14 represents a cross-section taken 2.5 cm. above the level of the proximal plane of section at six weeks. Note the enormous number of non-medullated fibers, interspersed among the medullated. Some are derivatives of non-medullated fibers, and some of medullated, as is illustrated in Fig. 15, in which (*a*) points to a subneurilemmal plexus derived from the medullated axone by lateral branching, and (*b*) to a bundle derived from a non-medullated one. All fibers of regeneration are at first non-medullated. Persistent nerve fibers grow down, as we have seen, into the protoplasmic bands of the tube as early as the fifth and sixth days. Fig. 17 gives a detail from the intermediate (regenerated) segment at six weeks. Note the bundles of non-medullated fibers. Many of them as (*a*) illustrate the fact that the medullated fibers, in regenerating, not only give rise, higher up, to numerous lateral rami, that course down just beneath the neurilemma, or, better, within the protoplasmic band of the neurilemma, but also that the stump of the old central axone also grows down as one (or sometimes several) fibers. Fig. 16 shows the proximal stump just above the plane of section after 8½ weeks. Note the remnants of swollen degenerated medullated axones (*a*), and the large bundles of non-medullated fibers. Fig. 18 illustrates the fibers growing down through the intermediate segment. Note the arrangement in bundles. End-bulbs are seen on the growing tips of some of the fibers. Fig. 19 is from the intermediate segment and illustrates the arrangement in bundles, the fibers of which course along a single protoplasmic band. Note the deflection of some bundles corresponding with anastomoses of bands. The invasion of the distal segment by the regenerating fibers, as seen in silver preparations, is illustrated in Fig. 20 (four weeks), and in Fig. 21 (seven weeks).

Fig. 26 illustrates a phenomenon we have often observed in the distal stumps; namely, the persistence of certain elements of the old sheaths, as manifested in old resting nuclei (*a*) and fibrous connective-tissue strands, surrounding the sharply marked bundles of new fibers, mostly non-medullated (*b*) and hence appearing glistening white, and not sharply defined in the microphotograph; some, however, having acquired the new medullation (*c*). Interspersed among these fibers are the new (hyperplastic) neurilemmal nuclei (*d*). The resting nuclei (*a*) are either neurilemmal or connective-tissue nuclei—we are not yet certain which. If the former, then, it would appear that in the several weeks which elapse, in the case of a large defect, before axis-cylinders from the central stump reach the distal canals, the neurilemmal bands may go through their stage of hyperplasia and then revert to the resting stage, and that neurilemmal sheaths from higher up (as from the distal level of Section 1) may grow down with the axone. We suspect, however, that these resting nuclei (*a*) belong to the connective-tissue sheath of Henle.

The hyperplasia of neurilemmal nuclei persists a very long time. Langley and Anderson (1904) have already noticed this. Fig. 27 shows them in the distal segment after 30 weeks. The nuclei which are yet very large, hyperchromatic and numerous, are applied to the non-medullated and medullated fibers, of course in a subneurilemmal position. Fig. 26 also illustrates the persistence of embryonic neurilemmal nuclei (*d*) after 27 weeks.

Biologic Interpretation of Neurilemmal Hyperplasia.

The hyperplasia of neurilemmal cytoplasm and nuclei has been recently interpreted by certain authors as a degenerative phenomenon, occurring only in a nerve undergoing "progressive retrogression," this interpretation being based largely upon experimental work in which neurilemmal hyperplasia was

absent in moderate grades of axis-cylinder and myelin degeneration, and present in severe grades, as also in advanced generalized degenerative processes, for instance, in gangrene of an extremity. But, in observing the processes, both the rapid degeneration in the immediate proximity of the section, and the slower Wallerian degeneration, we cannot but be struck by the intimate association of retrogressive and progressive processes. As V. Büngner (1891) says: "The processes of degeneration and regeneration are so closely associated, both as to spatial and temporal relations, that they defy any separate consideration, occurring simultaneously and in the closest proximity."

Yet it is possible, just as in the case of the phenomena of inflammation, to be sure that certain phases of the complex process partake of the general nature of a degeneration, catabolic changes predominating excessively (as the disintegration of axis-cylinder and myelin); and we may be just as certain that a process in which, starting with a mechanical stimulus, we observe a reversion of the adult, resting, neurilemmal nuclei to an embryonic condition, with hyperchromatosis, mitotic activity, nuclear migration, increase of cytoplasm, to say nothing of probable metabolic activity with reference to absorption of dead myelin, is of a regenerative or hyperplastic nature. Certainly in the domain of pathology, where this whole matter has received minute consideration with special reference to the components of the general process of inflammation (see, for example, Ribbert, *op. cit.*, p. 209), no one would think of classifying the fibroblastic proliferative responses as degenerative in character, however markedly retrogressive the general reaction of which they form a part. The concepts of local and general degeneration are not to be confused.

Some of those workers that have maintained the degenerative character of the hyperplasia have apparently been influenced by the consideration that, if the neurilemmal hyperplasia were a regenerative process, the doctrine of peripheral regeneration would be thereby strengthened. But such is by no means the case. The problem—whether the protoplasmic bands have in themselves the inherent property of depositing axis-cylinders—is entirely independent of the hyperplastic character of these bands, and must be settled inductively. Biologically, then, in the light of modern concepts of regenerative and degenerative processes, the proliferation of neurilemma is purely hyperplastic or regenerative.

Nageotte (1915) hints at some special, mutual interdependence of neurilemma and axis-cylinder, but we believe the observations recorded in the present paper show that the sheath is to be regarded as a structure *per se*, independent of any essential genetic relation to the axis-cylinder. In response to mechanical or chemical (toxic) stimuli, it may undergo hyperplasia with reversion to an embryonic state. In so doing, it may and does serve as a conduit for regenerating cylinders. We do not doubt that the latter, under clinical conditions as in certain traumatic nerve injuries, often attempt to push out into ordinary cicatricial tissue, but on leaving the neurilemmal territory that portion of the fiber usually—perhaps always—succumbs. Probably this is simply a mechanical sequence.[1]

With reference to the mutual relationship between neurilemmal hyperplasia and the closely associated degeneration and absorption of axis-cylinders and myelin there have been many speculations.

It is generally conceded that the granular degeneration of axis-cylinder and of myelin are the earliest of these processes to begin. The death of the axis-cylinder is probably a trophic sequence of isolation from the ganglion cell. Many authors (*e. g.*, Nageotte and Cajal, 1911) hold that the myelin digests the dead axis-cylinders. Of course, numerous observers have shown that fragments of axis-cylinders are enclosed within the "ovoids" or segments of the disintegrating myelin, but no satisfactory proof is as yet available that the myelin digests the dead axis-cylinder. Dr. Bensley, in a recent personal communication, points out that modern concepts of the inherent enzymatic autodigestive powers of all tissues render superfluous such assumptions, except where definite evidence exists. V. Büngner (1891) took a similar conservative position with reference to the disintegration of the myelin which he considers to be a passive process. He also shows that migratory leucocytes have no place in the absorption. Nageotte (1911) states that the chemical products of the degenerating axis-cylinders and myelin furnish the efficient stimulus to the neurilemmal-sheath hyperplasia. Ingebrigtsen (1916) believes that his work confirms Nageotte's idea, for growth of neurilemmal cells in plasma was obtained only when Wallerian degeneration (of axis-cylinders and myelin) had begun in the nerve before its introduction into the plasma. But to insure this, the nerves after section were allowed to remain *in situ* for the four or more days. This, however, introduces a confusing factor, for during those days the neurilemma takes on a very hyperplastic condition. Ingebrigtsen's work, far from showing that the disintegration products of dead axis-cylinders and myelin stimulate the neurilemma to proliferate, indicates that neurilemma, in reverting to this embryonic condition, acquires greatly increased viability and growth potentiality. The fact that the neurilemma, after four days of hyperplasia in the body, grows out into typical protoplasmic bands, morphologically almost identical with those we describe, offers confirmatory evidence as to our conception of the early development of true bands at the traumatized stump.

Moreover, Clark repeatedly obtained marked degrees of degeneration in axis-cylinders and myelin without stimulation of the neurilemmal sheaths to hyperplasia. Also, Ranson proved that protoplasmic bands develop from non-medullated fibers in the distal stump.

There does, however, appear to be evidence that the hyperplastic neurilemmal cytoplasm helps in the absorption of the degenerated myelin and axis-cylinders. Howell and Huber (1892) offered good morphologic proof of this. Clark also

[1] In this sense the dictum of Bethe may be true: "Die Ganglienzelle allein besitzt überhaupt nicht die Fähigkeit einen neuen Neuriten zu bilden. Damit ein neuer Neurit vorwachst, muss die Ganglienzelle in Verbindung mit Schwann'schen Zellen stehen."

notes that when the neurilemma displayed no reaction, the remnants of axis-cylinders and myelin globules persisted months or over a year unabsorbed, whereas, in the cases in which neurilemmal hyperplasia was produced, they were rapidly absorbed.

Thus, aside from the traumatic factor, which admittedly is of minor importance, we know nothing satisfactory as to the causes of neurilemmal hyperplasia.

Monogenetic Origin of Axis-Cylinders.

It would be superfluous to discuss the enormous literature regarding the doctrine of peripheral regeneration. In general the overwhelming tendency of modern work has been to show that all definitive regeneration of nerve fibers is from the central segment.[5]

Ranson's work offers especially reliable evidence of this. Clark (1914) confirms it also, as regeneration of axones was often complete in his experimental neuritis in the absence of neurilemmal hyperplasia and protoplasmic band formation.[6]

Ingebrigtsen (1913 and 1916) has shown that *in vitro* the axis-cylinders grow only from the ganglion cell or from the central stump of an axone.

On employing this tubulization technique it soon became apparent that we had an excellent opportunity for investigating the possibility of a peripheral regeneration of axis-cylinders. The limits of the present paper prevent the inclusion of details, but, in brief, it is certain that no axis-cylinders appear in the distal segment, until they have grown down in continuity from the central stump, having bridged the gap. The Cajal-Ranson silver method has ensured against confusion of other types of protoplasmic fibrillation with true axis-cylinders.

Origin of Myelin Sheaths.

The limits of this paper forbid our presenting the detailed results of our study of this question by the tubulization method.

We can, however, confirm the general observation of Howell and Huber (1892), of Mott, Halliburton and Edmunds (1904) and of others, that myelin formation proceeds from the distal end of the proximal segment downward. Inasmuch as all these observers approximated their nerve ends, an element of confusion was introduced, as indicated in the conclusion of Halliburton and Edmunds that the myelin formation starts from the point of union of proximal and distal stump and proceeds distally.

We find, as did Stroebe (1893), that the myelin sheath is formed in continuity with the original myelin sheath above, *i. e.*, the first new myelin to appear is that which restores the myelin of the proximal stump that early underwent an ascending degenerative process. Thus it appears at successively more distal levels, and only when the regenerated axis-cylinder has reached the age of about five or six weeks.

[5] *Vide* Ranson, 1912, for an excellent review.

[6] Bethe and other exponents of peripheral regeneration hold that the nerve fibers are laid down within the protoplasmic bands.

Fig. 22 shows a control, the segment removed from a normal nerve at operation—stained with phosphotungstic acid hematoxylin. The myelin sheaths (*a*), shown in white in the microphotograph, are stained a bright blue. The darker areas represent bundles of non-medullated fibers (*b*) and endoneural connective tissue (*c*).

Fig. 23 represents the same nerve seven weeks after operation, the level represented being in the proximal segment about 3 mm. above the plane of section. Some of the medullated fibers are slightly swollen, but the great majority are of normal size or smaller, some not more than one-quarter the diameter of the largest. Note particularly the large bundles of non-medullated fibers (*b*) with closely associated neurilemmal nuclei (*c*). These are, of course, the bundles of regeneration.

Fig. 24 is from the same nerve at the upper part of the regenerated (intermediate) segment. Each bundle is composed largely of non-medullated axis-cylinders (*a*), which do not show in detail in the photograph, but each contains also neurilemmal nuclei (*b*) and fibers which have newly acquired myelin sheaths (*c*). These latter are very delicate, but are stained a bright blue by the Mallory stain and present the usual radiate appearance of the neurokeratin framework.

Fig. 25 shows the same nerve at the lower part of the regenerated (intermediate) segment. Note that the bundles consist entirely of non-medullated fibers with associated neurilemmal nuclei. No medullary sheaths have reached this far distally.

Finally, Fig. 26 again shows the distal stump at 27 weeks, when the bundles of regeneration have long since filled up the old empty canals. Note that even yet a majority of the fibers in each bundle are non-medullated. Those which have acquired medullation seem perfect in morphology. Many neurilemmablasts yet persist, associated closely with the regenerated bundles.

Thus in the nerve shown in Figs. 22 to 25, inclusive, the upper 3 or 4 mm. of the regenerated segment contain at the seventh week of regeneration a considerable number of medullated fibers.

In nerves after nine weeks of regeneration, many of the fibers bridging a gap of 12 mm. have acquired a medullation throughout their extent and even some distance into the distal stump.

Interpretation.—The myelin is laid down *in situ*, whether by activity of axis-cylinder or of neurilemma we could not determine, but undoubtedly it appears only in those portions of the new fiber which have reached an age of about five or five and one-half weeks. All medullated fibers regenerate through the gap as non-medullated ones, which later acquire medullation. All medullation begins proximally and proceeds distally.

Many fibers acquire their medullation much later than the sixth week.

We have no reason to doubt the accuracy of Howell and Huber's observation of the discontinuous appearance of myelin within the protoplasmic bands, but certainly the general progression is from the proximal stump distalwards.

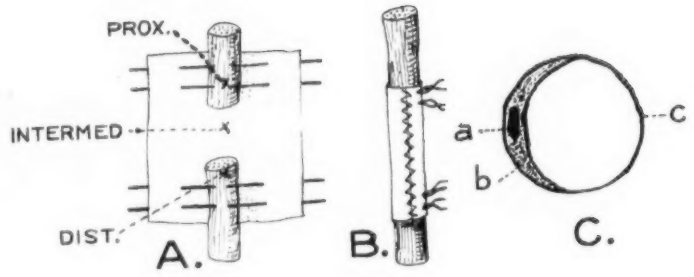

FIG. 1.

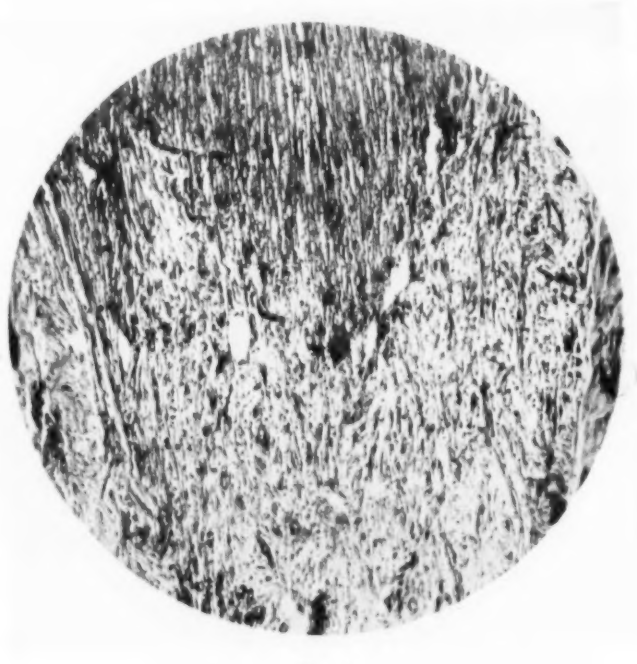

FIG. 4.

FIG. 2.

FIG. 3.

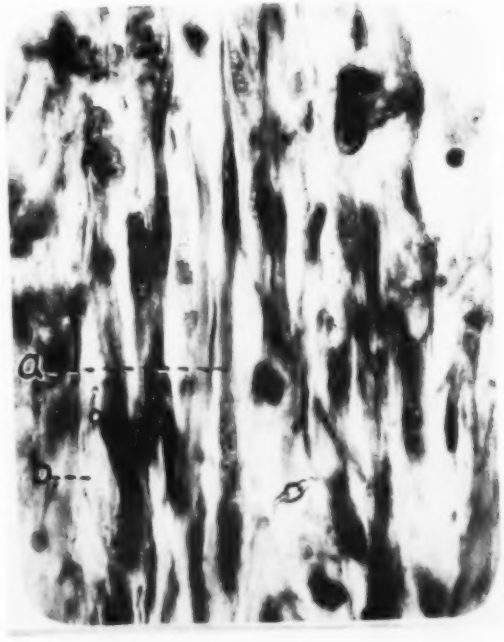

FIG. 5.

PLATE V.

FIG. 10.

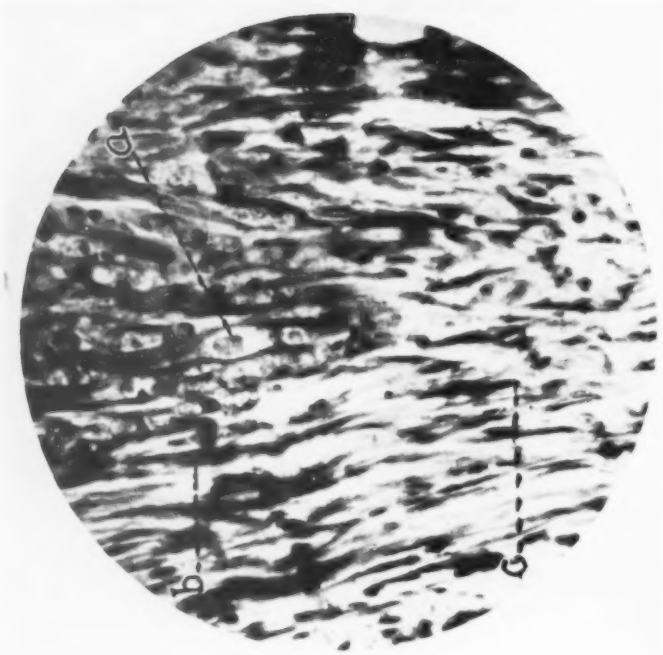

FIG. 6.

FIG. 9.

FIG. 8.

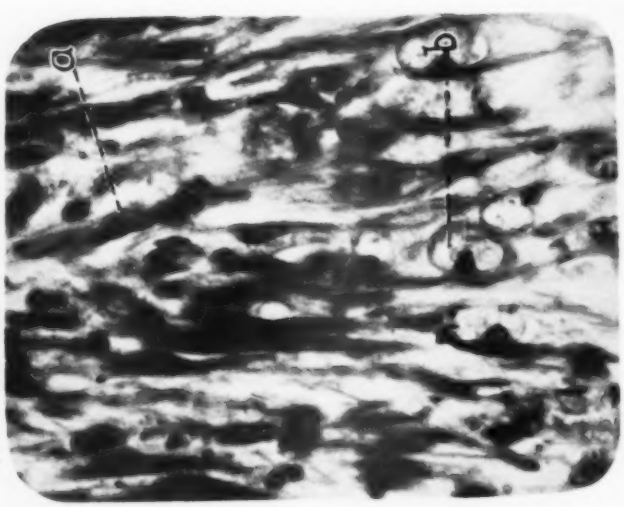

FIG. 7.

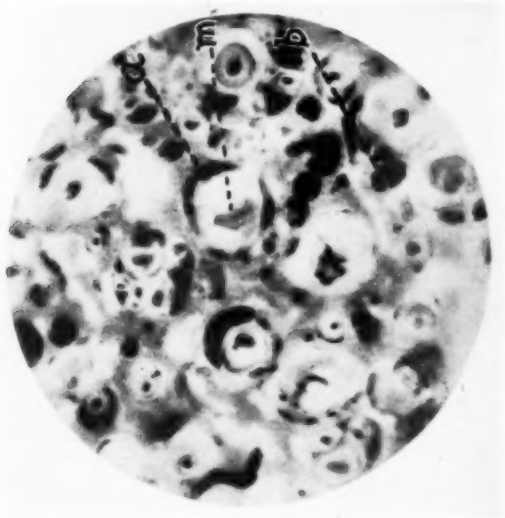

FIG. 9.

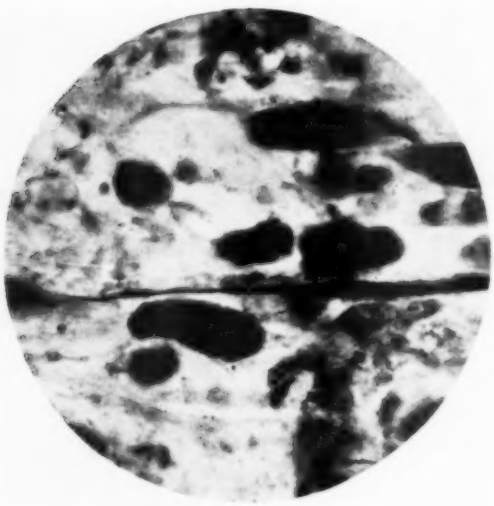

FIG. 8.

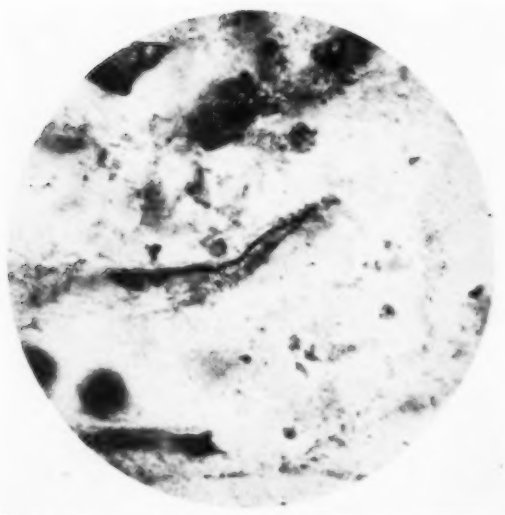

FIG. 7.

FIG. 15.

FIG. 14.

FIG. 12.

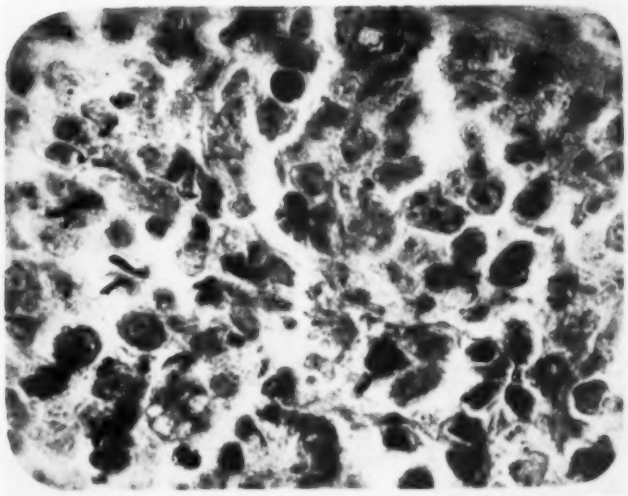

FIG. 13.

FIG. 11.

FIG. 16.

FIG. 17.

FIG. 18.

FIG. 19.

FIG. 20.

FIG. 21.

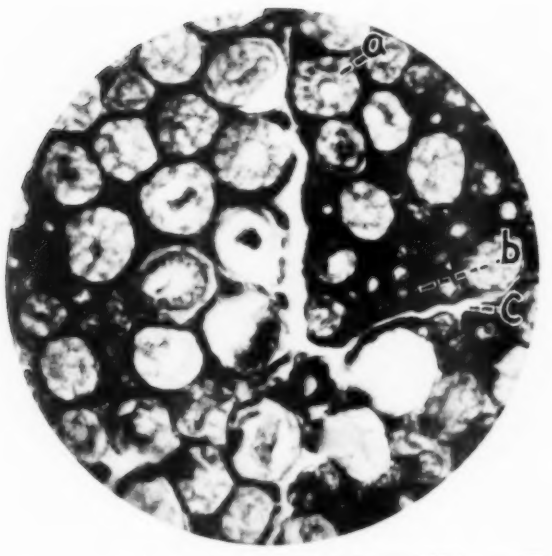

FIG. 22.

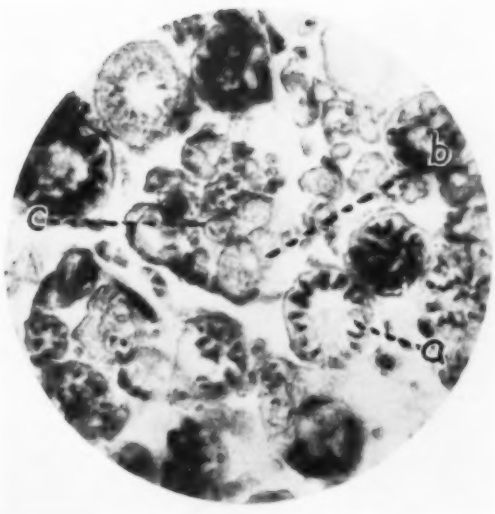

FIG. 23.

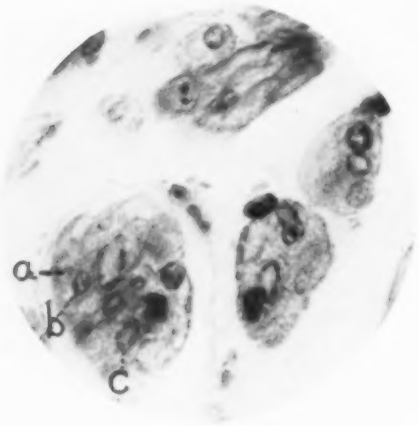

FIG. 24.

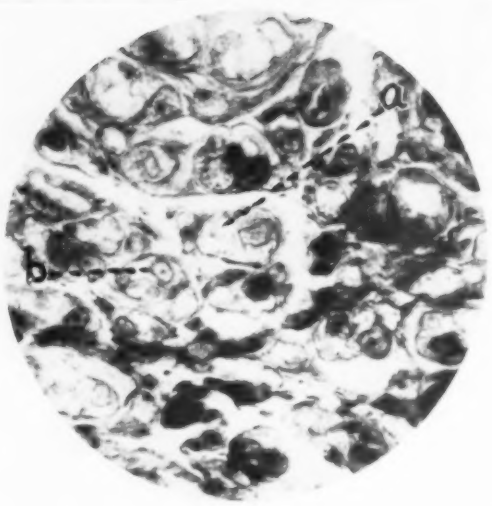

FIG. 25.

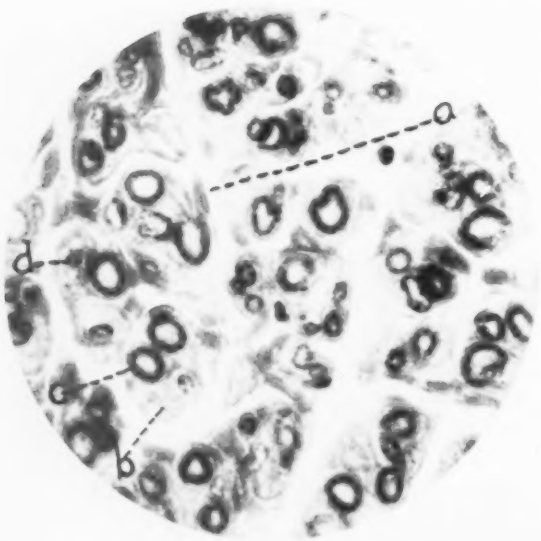

FIG. 26.

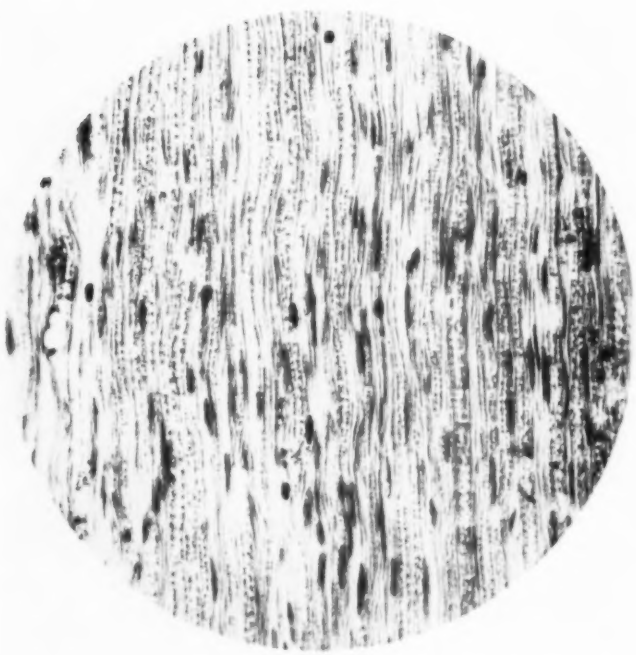

FIG. 27.

SUMMARY.

1. In the immediate vicinity of nerve trauma associated with break of continuity there occurs an accelerated hyperplasia of the neurilemmal elements which results in the early formation of protoplasmic bands. These develop in both proximal and distal stump and tend to bridge the defect. Along these protoplasmic pathways the regenerating axis-cylinders from the central stump pass. Whether they reach the distal stump and neurotise it depends largely on the extent to which these preformed conduits have successfully prepared the way.

2. All efficient regeneration of nerve fibers (axis-cylinders) is from the central stump. All regenerating nerve fibers, whether the outgrowth of medullated or of non-medullated axones, are in their early stages non-medullated.

3. All medullation begins proximally and proceeds distally, appearing only in those parts of the new axis-cylinder which have acquired an age of five or five and one-half weeks (in the dog).

LITERATURE.

Bethe: Arch. f. d. ges. Physiol., 1907, CXVI, 385.

Clark: Jour. Comp. Neurol., 1914, XXIV, 61.

Dustin: Münch. Med. Wchnschr., 1913, LX, 2252.

Harrison: Anat. Rec., 1908, I, 209.

Howell and Huber: Jour. Physiol., 1892, XIII, 335.

Huber: Arch. f. mikr. Anat., 1892, XL, 409.

Huber: Journal Morphol., 1895, XI, 629.

Ingebrigtsen: Jour. Exp. Med., 1913, XVII, 182; also, XVIII, 412; also, 1916, XXIII, 251.

Kirk and Lewis: Jour. A. M. A., 1915, LXV, 486.

Kirk and Lewis: Anat. Record, 1916 (Jan.), X, No. 3. (Abstract of paper read before Assoc. Amer. Anat., at Yale University, Dec. 28, 1915.)

Langley and Anderson: Jour. of Physiol., 1904, XXXI, 418.

Mott, Halliburton and Edmunds: Jour. Physiol., 1904, XXXI. Section on Proceedings, p. 7.

Nageotte: Compt. rend. Soc. biol., 1911, LXX, 861.

Nageotte: Compt. rend. Soc. biol., 1915, LXXVIII, 153 and 249.

Ranson: Jour. Comp. Neurol., 1912, XXII, 487.

Ribbert: Lehrb. der Allg. Pathologie, 1908.

Stroebe: Beiträg z. path. Anat., 1893, XIII, 160.

DISCUSSION.

DR. HOWELL: I hardly feel qualified to discuss Dr. Lewis's results, as it has been more than 25 years since I worked upon the subject. At the time when Huber and I were investigating the subject of nerve-regeneration there were still fond hopes that union of severed nerves might take place by first intention with immediate restoration of function. The picture presented by Dr. Lewis of the processes of regeneration is, in most respects, the same as we found and described, except in the matter of the down-growth from the central stump of protoplasmic bands, which precede and guide the development of new fibers. This seems to me a new and interesting observation. The suggestion, quoted from Clark's paper, that the formation of the embryonic fibers is a process of degeneration rather than of regeneration is, I believe, open to criticism. I do not see how you can avoid the conclusion that the regeneration is intimately connected with, and dependent on, the growth and proliferation of the neurilemmal nuclei. The augmented activity of these nuclei is the key-note to the whole process of regeneration. The great rapidity with which they multiply as the old fibers undergo fragmentation is in fact an extraordinary phenomenon. As Van Gehuchten has pointed out, nothing of this kind is observed in a dead nerve. The underlying conditions which lead to this new growth-activity have not been explained. We may assume as a provisional theory that it is due to some chemical stimulus developed in the process of degeneration of the old fiber or to the formation of specific growth-substances, but so far as I am aware we have no good experimental data in regard to this point.

DESCRIPTION OF FIGURES.

FIG. 1.—(A) Diagram illustrating method of tubulization. (B) Diagram of completed tubulization. (C) Diagrammatic cross-section of hyperplastic neurilemmal sheath: (a) Neurilemmal nucleus; (b) Protoplasmic band; (c) Non-hypertrophied portion of sheath.

FIG. 2.—Control normal nerve. Segment removed at primary operation, illustrating maximal normal number of neurilemmal nuclei. (×1000.) Phosphotungstic acid hematoxylin.

FIG. 3.—Proximal stump just above plane of section, at sixth day. To illustrate neurilemmal hyperplasia. (×1000.) Hematoxylin and eosin.

FIG. 4.—Proximal stump, at sixth day. To illustrate down-growth of neurilemmal (protoplasmic) bands into serum of tube. (×75). Hematoxylin and eosin.

FIG. 5.—Detail from Fig. 4, showing tip of proximal stump. Note—(a) protoplasmic bands containing neurilemmal nuclei; also (b) degenerated medullated fibers. (×750.) Hematoxylin and eosin.

FIG. 6.—Distal stump at sixth day. To illustrate proliferation of neurilemmal bands (b) in the nerve tip; also (c) the same growing in serum of tube; and (a) degenerated fragment of axis-cylinder enclosed in a globule of myelin. (×335.) Hematoxylin and eosin.

FIG. 7.—Detail from Fig. 6, showing tip of distal stump. Note—(a) protoplasmic bands in the serum; also (b) degenerated axis-cylinder and myelin. (×650.) Hematoxylin and eosin.

FIG. 8.—Detail from distal stump just below level of operative section, at sixth day. Note protoplasmic bands (a). (×1000.) Hematoxylin and eosin.

FIG. 9.—Detail from a point 10 mm. from proximal, and 2 mm. from distal stump at sixth day. Note protoplasmic bands (b) in serum of tubule; also migratory cells. (×750.) Hematoxylin and eosin.

FIG. 10.—Detail from growing tip of proximal stump at five and one-half weeks. Note protoplasmic bands with non-medullated axones, the latter stained black. (×1200.) Silver-pyridine method.

FIG. 11.—Protoplasmic bands containing non-medullated axis-cylinders, the latter stained black, from serum-filled tube just below proximal stump at sixth day. (×1200.) Silver-pyridine and safranin.

FIG. 12.—Protoplasmic bands with non-medullated axis-cylinder. (×1200.) Silver-pyridine and safranin.

FIG. 13.—Cross-section at tip of regenerating proximal stump at the eighth day. An area has been selected which shows some protoplasmic bands devoid of axis-cylinders, and some containing them. The latter stain black. (×1000.) Silver-pyridine.

FIG. 14.—Cross-section of proximal stump, 2.5 cm. above plane of surgical section at sixth week. Note great increase in non-medullated fibers. (×200.) Silver-pyridine.

FIG. 15.—Cross-section of proximal stump, 3 mm. above plane of surgical section at 31 weeks. Note non-medullated subneurilemmal plexus (a) derived from the medullated axis-cylinder (m) by lateral branching; also bundles (b) of non-medullated fibers, derivatives of a non-medullated axone. (×1000.) Silver-pyridine.

FIG. 16.—Detail from proximal stump at eight and one-half weeks. Note swollen myelin sheaths (a); also bundles of non-medullated fibers stained black. (×400.) Silver-pyridine.

FIG. 17.—Cross-section of intermediate segment (*i. e.*, the regenerated hiatus), at sixth week. Note bundles of non-myelinated fibers stained black. Group (a) is derived by down growth from a medullated axone. (×325.) Silver-pyridine.

FIG. 18.—Detail from intermediate segment at eight and one-half weeks. End bulbs are seen at growing tips of some fibers. (×325.) Silver-pyridine.

FIG. 19.—Detail from intermediate segment at the tenth week. Note arrangement in bundles. (×200.) Silver-pyridine.

FIG. 20.—Distal segment at fourth week. To illustrate invasion by regenerating non-myelinated fibers. (×130.) Silver-pyridine.

FIG. 21.—Distal segment at seventh week. (×70.) Silver-pyridine.

FIG. 22.—Normal control segment removed from nerve 39 at primary operation. Note (a) myelinated fibers: (b) bundle of non-medullated fibers; (c) connective tissue. (×1000.) Phosphotungstic acid hematoxylin.

FIG. 23.—Proximal segment of nerve 39 (same nerve as shown in Fig. 22), at seventh week after section. Note (a) medullated fibers, (b) bundles of non-medullated fibers and (c) neurilemmal nuclei. (×1200.) Phosphotungstic acid hematoxylin.

FIG. 24.—Same nerve (seventh week). Upper part of intermediate segment (*i. e.*, regenerated hiatus). The bundles consist largely of non-medullated fibers (a) but also contain a few fibers (c) surrounded by delicate myelin sheaths, staining a bright blue and also neurilemmal nuclei (b). (×1200.) Phosphotungstic acid hematoxylin.

FIG. 25.—Same nerve (seventh week). Lower part of intermediate segment. The bundles consist entirely of non-medullated fibers (a) with neurilemmal nuclei (b). (×1200.) Phosphotungstic acid hematoxylin.

FIG. 26.—Distal segment at 27 weeks. The bundles consist largely of non-medullated fibers (b) among which are some medullated, (c) and some neurilemmal nuclei (d), which are yet hyperplastic (*i. e.*, neurilemmablasts.) The resting nuclei (a) are probably connective tissue nuclei of the sheath of Henle. (×1000.) Phosphotungstic acid hematoxylin.

FIG. 27.—Distal segment of a nerve at 31 weeks after operation. To illustrate the persistent hyperplastic condition of the neurilemmal nuclei. (×450.) Phosphotungstic acid hematoxylin.

THE SIGNIFICANCE OF XANTHOCHROMIA OF THE CEREBROSPINAL FLUID.

By T. P. SPRUNT and J. E. WALKER.

(From the Medical Clinics of the City Hospital, Baltimore, and of The Johns Hopkins Hospital.)

In 1903, Froin [1] described in the cerebrospinal fluid from a patient with an organic nervous disease several peculiarities, a yellow color, an increased number of lymphocytes and a marked and rapid coagulation. This condition of the fluid has sometimes been called Froin's syndrome.

Froin [2] later added other cases and was followed by several of his compatriots, Aubrey,[3] Babinski,[4] Cestan and Ravaut,[5] Mestrezat,[6] and others. Considerable interest in this condition has been shown by German writers, as evidenced by many articles in the years from 1909 to 1914 by Schnitzler,[7] Siemerling,[8] Klieneberger,[9] Raven,[10] Oppenheim,[11] Nonne,[12] Schlesinger,[13] and others. More recently in English and especially in American literature we find several references to the subject, notably those by Cooper,[14] Greenfield,[15] Hartman,[16] Kennedy and Elsberg,[17] Collins and Elsberg,[18] Mix,[19] Campbell,[20] Horrax,[21] Bromer,[22] Hanes.[23]

In different cases there are variations in the amount and rapidity of clot formation, in the presence or absence of lymphocytosis and in the amount of globulin. Owing to the difference in points of view or in methods of examination certain observers in describing what is probably the same type of fluid emphasize some of these characteristics and neglect to mention others. In general the Germans are interested in the large amounts of globulin—the Positive Phase I of Nonne—and frequently say nothing of coagulation, whereas the French lay stress upon the coagulation *en masse* and may make no mention of the presence or absence of globulin or cells. Hence we feel that in tabulating cases for study we should not make the criteria too strict nor attempt to conform too rigidly to the description of any one author, as Mix [19] seems to have done in insisting upon massive coagulation as a necessary feature of the syndrome.

It is generally recognized that a yellow color may occur in the spinal fluid after a hemorrhage into the ventricles or the subarachnoid space when the cells may have almost or entirely disappeared, and also in purulent or in tuberculous meningitis. In such cases, however, the condition can rarely be confused with the syndrome under discussion, if the other available data are considered.

Practically all authors agree that for the production of this syndrome there is necessary an interruption to the flow of the cerebrospinal fluid, and the formation of a pocket of greater or less extent in which the fluid stagnates and into which various elements pass by transudation from the blood vessels within its walls. Hence one can appreciate the value of such a finding in certain cases of compression of the spinal cord.

The following cases stimulated our interest in this and other types of fluid in compression of the cord, especially the syndrome of Nonne, or, as he speaks of it, Isolated Phase I,[24] to which we shall again refer.

CASE 1.—*G. A., white, tailor, aged 41, admitted to the City Hospital, June 30, 1915, and discharged June 27, 1916. Med. No. 2950. Tumor of cauda equina. Operation with partial removal; subsequently, treatment with radium; improvement.*

The patient complains of "neuritis of both legs." The family and past histories are negative. The present illness began 9 years ago, in 1906, with a sudden pain in the right leg, which increased rapidly in severity and in distribution, extending down the right leg and into the left hip. After an operation on the right sciatic nerve the pain subsided and the patient was able to return to work for 4 years during which there was no trouble

except transient pain in the lumbar region. Five years ago there was another sudden outbreak of pain in both legs which has become progressively worse except for slight remissions. He has been unable to work for 3 years, and unable to walk for 10 weeks. Wasting of the leg muscles began about 3 years ago; occasional retention of urine 2 years ago. There have been numbness and tingling of the feet for several years and a gradual loss of weight of 50 pounds. The pains were so frequent and so severe that the patient got very little sleep.

Physical examination showed an evidently pain-racked, emaciated man, unable to walk, and unable to move in bed without pain and considerable effort. His mentality was clear and the internal organs were not evidently diseased. The spine was held stiffly with practically no flexion or extension, and with only slight lateral motion and very little rotation. The lumbar region was especially rigid and the usual lordosis obliterated. The 12th thoracic and 1st and 2d lumbar spines were a little tender, and there was a more sensitive point just to the left of the 2d lumbar spine. The cranial nerves were normal; the muscular strength in the neck, arms and body was fairly good and the deep reflexes were moderately exaggerated. In the lower extremities there was little complete paralysis, but the muscles were very weak, extraordinarily wasted and flabby and showed numerous fibrillary tremors. There was bilateral foot-drop, complete on the right. The deep reflexes were practically abolished; Babinski's sign was not present in the left foot and there was no response whatever to plantar stimulation of the right. The abdominal and cremasteric skin reflexes were active. No anal reflex was obtainable. The gluteal muscles were atrophic and showed fibrillary twitchings. There was marked impairment of pain, temperature and tactile sensation over the whole of the right foot and the lateral surface of the right leg half way to the knee, and slight impairment above this in front almost to the knee and over the dorsum of the left foot. The deep muscle sense was absent in the right foot. Examinations of the rectum, the stools, the urine and the blood were negative. The X-ray plate of the lumbar spine was negative.

Two lumbar punctures at an interval of about 2 weeks were considered unsatisfactory. Only a few drops of fluid were obtained the first time and less than a cubic centimeter the second time. The fluid was very viscid, of a yellow color and contaminated by fresh blood. It clotted immediately into a jelly-like mass, so that the tube could be inverted without spilling its contents. On the third attempt, 2 cubic centimeters were obtained under very low pressure, the fluid falling from the needle drop by drop. It was perfectly clear, of a lemon yellow color and slightly oily in appearance. Minute globules of an oily substance adhered to the sides of the tube. After about 3 minutes a pale yellow clot began to form and in 5 minutes occupied half the volume of the fluid. The clot had remained unchanged in size 2 days later. The reaction for globulin was strongly positive. With the spectroscope no absorption bands were seen. The Wassermann test of the fluid, as of the blood serum, was negative. Microscopical examination showed no leucocytes, and only 2 or 3 red blood cells in many fields, a few irregularly shaped structureless pieces of material, and many globules of varying sizes, very highly refractile, which stained intensely with Sudan III. With the polarizing microscope, many of these globules were definitely doubly refractile.

The diagnosis was made of an intradural, extramedullary tumor involving the roots of the cauda equina, and on Sept. 28, laminectomy was done by Dr. Arthur M. Shipley. A very vascular, soft, purplish mass was found covering the cauda and extending along the nerve roots. At a second operation, one week later, much of the very friable tumor mass was removed, but a large part of it necessarily remained. Microscopic study showed that the tumor was a glioma. Convalescence from the operations was satisfactory and the patient's pain was greatly ameliorated, although very little objective improvement was manifest for several months. By April, there were definite evidences of improvement; the area of anæsthesia had become a little smaller, some power of voluntary movement had returned in the toes of the right foot and the patient was able to walk a little with assistance.

In May and again in June, 1916, through the courtesy of Dr. Burnam, he was treated with radium over the lumbar spine. At the time of his discharge, the patient had no pain; he was able to walk with the help of crutches, and had gained many pounds in weight. There were still a few fibrillary twitchings in certain muscles, tenderness over the tumor site and almost complete paralysis and anæsthesia of the right foot. Reports 2 months and 3 months after discharge were encouraging.

CASE 2.—*W. H., white, student, aged 15, admitted to The Johns Hopkins Hospital, Oct. 23, 1914; discharged Nov. 23, 1914. Medical No. 33225. Multiple sarcomata of the spinal cord; exploratory laminectomy; death 2 months after discharge from hospital.*

The patient complains of nervousness. His family and past histories are negative. The present illness began 6 months before with an injury to his right shoulder and chest, which was not considered serious. Ten days later pain began in the upper portion of the right chest; later it extended downward and appeared also in the left scapular region. Six weeks ago the left leg became numb, and this was followed after 2 weeks by similar sensations in the right leg. During the past 3 weeks, there has been weakness in the legs, marked nervousness and stiff neck. The pain disappeared.

Physical examination showed a fairly well nourished boy and, other than neurological, was negative. There was slight nystagmus and a slight tremor of the tongue. The eye-grounds were negative. There was no limitation of movement in the cervical, thoracic or lumbar regions of the spine and no tenderness over the spine. A jaw-jerk was present and the deep reflexes in the arms were exaggerated. The abdominal skin reflex was absent except in the left lower quadrant. Weakness in the leg muscles, especially on the right, was evident with definite hypertonicity but no atrophy. The gait was spastic, the knee-jerks were greatly exaggerated, with a well sustained ankle and patellar clonus on both sides and bilateral positive Babinski and Oppenheim phenomena. There was definite hypæsthesia below the level corresponding to the 3d thoracic segment, but no hyperæsthesia or absolute anæsthesia. There was no sphincter disturbance.

Examinations of blood, urine and stools were negative. X-ray plates of the cervical, thoracic and lumbar spine were negative.

Lumbar puncture: Ten cubic centimeters of perfectly clear, yellow, straw-colored fluid were obtained under a pressure at first of 100 mm. It clotted completely on standing so that the test-tube could be inverted without spilling the fluid. Before clotting, there were 61 cells per cubic millimeter, all mononuclears. The Ross-Jones test was strongly positive. The guaiac reaction and spectroscopic examination were negative. The Wassermann tests of fluid and blood serum were negative.

Diagnosis. Compression of spinal cord in upper thoracic region, probably by a tumor. An exploratory laminectomy, by Dr. Heuer, of the first four thoracic vertebræ, revealed a very vascular dura. When it was opened, the arachnoid did not bulge as a distinct layer, as is usual, but was evidently filled with the tumor, to which it was quite adherent everywhere. When the arachnoid was pricked, there was only a trace of fluid, and neither above nor below could fluid be encountered. Four distinct tumor masses were seen on the dorsal surface of the cord, one at the highest exposed portion extending across the cord. The remaining tumors almost filled the space to the lower limit of the exposure. One of them, the size of a hickory-nut, which was attached by a small pedicle, was removed for microscopical examination. The tumors had a glossy, friable appearance and were evidently sarcomata.

The microscope showed a very cellular, quite vascular tumor with little stroma. The cells were round or pear-shaped with many mitotic figures—the typical picture of a round-cell sarcoma.

After the operation sphincter control was lost, but was regained after a few days. Catheterization became necessary. Decubitus ulcers began to develop. The patient left the hospital in the ambulance and died 2 months later, completely paralyzed from the neck downward.

CASE 3.—*A. G., white, Pole, aged 41. Admitted to the City Hospital, Oct. 5, 1915, and died Nov. 9, 1915. Retroperitoneal metastasis from malignant tumor of the testis; extension through the lumbar and thoracic vertebræ; compression of spinal cord; autopsy.*

The patient complained of pain in the leg and back. Three years before admission, there had occurred a slight injury to the left testis which soon began to increase a little in size. One year before admission the rate of growth became more rapid until, in Nov., 1914, there was a tumor as large as a cantaloupe. This was removed in the Urological Department of The Johns Hopkins Hospital. There had been a loss of 50 pounds in weight.

(On investigation, it was learned that retroperitoneal metastases had been recognized at the time of operation and had been considered too extensive to justify a radical procedure.)

The present illness had begun in the summer of 1914 with pain in the lumbar region. This had become worse after the operation, and had soon appeared in the left leg, and after several weeks in the right leg also. The legs had then become progressively weaker and for 3 weeks before admission the patient had been quite unable to walk. Paræsthesias in both legs, slight swelling of the feet, some sphincter disturbance and loss of libido and potentia had been noted for several weeks.

Physical examination showed an emaciated man evidently in considerable pain, which was increased on any attempt to move. The patient lay constantly in a semi-recumbent position which made examination of the abdomen somewhat difficult. There was fairly marked rigidity of the abdominal muscles, slight diffuse tenderness and a hard, palpable mass in the left hypochondrium. This mass caused a bulging of the lower thoracic wall on the left side which was especially well seen in the back. There was both scoliosis and kyphosis of the lumbar spine with the convexity to the left and the apex at the 2d lumbar spine. There was also a definite gibbus, of which the second lumbar spine formed the most prominent point. Tenderness over the 1st, 2d and 3d lumbar spines was present.

The left testicle was missing and near the operative scar in the left inguinal region there was a small nodule about the size of an olive.

Bilateral foot-drop was evident; very little voluntary movement was possible in the left leg, and the right leg was very weak. Atrophy was not marked and there were no fibrillary tremors. The knee-jerk was absent on the left, very sluggish on the right; ankle-jerks were not elicited. There was no response to plantar stimulation. The abdominal, cremasteric and anal reflexes and the deep reflexes of the upper extremities were present and equal. There was marked impairment of epicritic sensation over the dorsum of both feet and a zone of hyperæsthesia pointing to the 12th thoracic segment.

Lumbar puncture. The fluid was under very low pressure: Four cubic centimeters were obtained, of a pale yellow color. A thin web-like clot formed after standing for 12 hours; the globulin reactions were strongly positive; the guaiac and spectroscopic tests were negative. Microscopically, there were 3 lymphocytes to the cubic millimeter. There were many doubly refractile droplets staining with Sudan III.

Three weeks later, when the symptoms of compression were much further advanced, another puncture was done. This fluid was water clear, under very low pressure, and contained 12 cells per cmm. The Ross-Jones and Pandy reactions were faintly positive. No droplets were found like those seen in the first specimen, nor were any abnormal cells discovered.

The blood, urine and stools were not significantly abnormal; phthalein excretion 42% in 2 hours; Calmette 1% negative; Wassermann negative. During the month in the hospital, the mass increased rapidly in size; the edema of the legs increased, fluid collected in the knee-joints and in the abdominal wall; the paralysis of the legs became complete and 3 weeks after admission the whole body below the level of the xiphoid was completely anæsthetic. One week later, the anæsthesia reached the level of the nipples. The temperature was irregularly intermittent, often reaching 103° F. Death occurred on Nov. 9, 1915.

Autopsy No. 652. Anatomical diagnosis. *Primary:* Operation, removal of malignant tumor of testis: metastasis to retroperitoneal lymph nodes with extension to bodies of lumbar and lower thoracic vertebræ; extension into spinal canal with compression of cord; infiltration of nerve roots of cauda equina; invasion of left renal pelvis; hydronephrosis and atrophy; extension into vena cava with propagated thrombus distal to tumor mass; compression of abdominal aorta.

Subsidiary: Chronic bronchitis; organizing bronchopneumonia; decubitus ulcer.

CASE 4.—*G. H., white man, age 57, admitted to the City Hospital, Sept. 6, 1916; transferred to the Surgical Service Sept. 8; died Oct. 9, 1916. Fracture of spine in lower thoracic region with marked displacement: flaccid paraplegia.*

The patient complained of "loss of the use of the body below the pit of the stomach." The family and past histories were negative. The present illness had begun with a fall from a wagon 8 days before admission. He had fallen on his back, and could not get up, had soon become unconscious and had been carried to his home. Examination showed a well nourished man in no acute pain. The abdomen was symmetrical, with distended, tortuous veins on the left side, tenderness on pressure in both upper quadrants, a palpable liver and a distended bladder. There was a sharp kyphosis at the level of the 12th thoracic vertebra with a correspondingly marked depression just below this point. The cervical and dorsal vertebræ showed perfect alignment, and from the 2d lumbar downward the vertebræ had preserved their normal interrelationships. The axes of the two portions, however, were not the same; the upper end of the lumbosacral portion was displaced markedly to the right. There was incontinence of urine and feces; the lower extremities were completely paralyzed with absence of deep reflexes, no response to plantar stimulation, and complete anæsthesia below the level corresponding to the 9th thoracic segment.

Lumbar puncture between the 3d and 4th lumbar spines gave a clear, amber fluid under somewhat decreased pressure. The globulin reactions were very strongly positive: there was no coagulation. The guaiac reaction was positive and the spectroscope showed the absorption bands of oxyhemoglobin. There were no red blood cells, but 16 mononuclears per cubic millimeter. The Wassermann tests on the blood serum and fluid were negative.

The patient lived for several weeks and died Oct. 9, 1915. At autopsy, the only significant lesions were fracture of the 11th thoracic vertebra with marked displacement and complete destruction of the spinal cord at this level.

We have reported in some detail 4 cases that showed the so-called Froin's syndrome in the cerebrospinal fluid, 2 cases of neoplasm of the cord or its membranes, 1 of a secondary tumor involving the vertebræ and spinal canal, and 1 of traumatic fracture of the vertebral column with displacement in the lower thoracic region. The duration of disease in the

different cases varied greatly, 9 years in 1, 1 year in another, 6 months in another and 1 month in the last case.

The fluids were essentially similar with minor variations, and were characterized particularly by clear transparency, yellow color, strong globulin reactions and low pressure. Spontaneous coagulation occurred in all except Case 4, either immediately or after standing a short while. There was an increased cell count in Case 2, but in none of the others. Case 4 was complicated by the hemorrhage which necessarily occurred with so much displacement of the vertebræ and the consequent laceration of the cord and its meninges, but in the other 3 cases tests for hemoglobin derivatives were negative. The occurrence of the doubly refractile droplets of myelin seems to be very unusual. The only similar observations of which we know are those of Krönig,[25] who found myelin droplets and larger fragments of tissue in the fluid from cases with areas of cerebral softening that had ruptured into the subarachnoid space. Degenerating tumor cells have been described a number of times and cholesterin crystals[26] at least once. The oily character of the fluid in our first case was evident on gross inspection and the droplets formed a striking part of the microscopic picture. Tumor cells were observed in none of our cases.

It cannot be said that the character of the fluid was a necessary factor in the diagnosis of any of our cases. But, as a matter of fact, our first patient had been set aside as the victim of a system disease, for which little could be done; and it was the unusual spinal fluid which reawakened our interest and led to the correct diagnosis, which should have been made without the assistance of the fluid.

The 4 cases show well the anatomical basis for the formation of such fluids as well as some of the different pathological processes by which it may be brought about. In 2 cases, there were intradural extramedullary tumors which completely filled the subarachnoid space and effectually shut off the spinal fluid below the lesion. In Case 3, a metastatic extradural tumor brought about the same result, and in the fourth instance the fracture with very marked lateral displacement in the lower thoracic region severed all communication between the two portions of the subarachnoid space. In addition, the presence of vascular tumors within the dura in 2 cases doubtless facilitated exchanges between intravascular and subarachnoid fluids. In the traumatic case, dissolved hemoglobin doubtless contributed to the color of the fluid and, in our opinion, accounted for its darker tint. The globulin, however, was increased to a much greater extent than the amount of blood alone would explain.

In our review of some 100 cases from the literature we find that almost all that have been sufficiently studied anatomically at operation or autopsy have shown this obstruction in the subarachnoid space. Tuberculous spondylitis,[1 10 22] intradural tuberculous granuloma,[23] extensive adhesions between cord, arachnoid and dura in cases of meningo-myelitis,[6] and gumma of the meninges,[12] are some of the other lesions responsible for such obstructions. Mestrezat[6] insists that the main determinants are the isolation of the lumbar cul-de-sac and vascular alterations within its walls.

There are some exceptions which are difficult or impossible to explain on the basis of compression and obstruction, but they usually show variations from the complete syndrome in the absence of spontaneous coagulation or of increased globulin or of both. A brief discussion of these cases follows:

1. Siemerling's[5] case of gliosis spinalis with syringomyelia is an apparent rather than a real exception, since the gliosis in the cervical region was really an intramedullary tumor of unusual dimensions and probably large enough to obstruct the subarachnoid space.

2. Schnitzler's[7] case of myelitis funicularis is more difficult to understand. At autopsy, besides the myelitis, only a deep scar was found in the lumbar region, the cause of which was not determined. The fluid was described as in small quantity, and intense lemon yellow in color; globulin was present, the lymphocytes were increased, but there was no coagulation; and tests for blood were negative.

3. Kennedy and Elsberg[11] describe a fluid "of light yellow color; globulin present, lymphocytes increased, 20 cells to the cubic millimeter" in one of their 5 cases of a peculiar disease of the cauda equina, in which the nerve roots were swollen, congested and a bluish-red color. They make no mention of coagulation or of tests for hemoglobin derivatives. This should probably be included among the cases in our fifth exception.

4. Three cases[1 19] are described as clinically resembling Landry's paralysis. One[27] of the patients recovered after 3 months. No autopsies were held in the other cases.

5. Finally there is a larger group of 8 or 9 cases,[21 28] usually of brain tumors in contact with the meninges or ependyma of the ventricles, in which the yellow color and other abnormalities in the fluid may be explained by repeated, small hemorrhages into the subarachnoid space. Spontaneous coagulation is usually lacking, the globulin is small in amount, the pressure is normal or increased, and there are crenated red blood cells or positive tests for hemoglobin. Such fluids may be perfectly clear or slightly turbid. These features with the clinical data usually distinguish such cases sufficiently. This type of fluid is probably more common than the number of published reports would indicate.

As examples of this type, the following cases are reported briefly:

CASE 5.—*K. N., white woman, age 37, admitted to City Hospital, March 23, 1916; discharged April 1, 1916; admitted to the University of Maryland Hospital, Sept. 8, 1916, and died Oct. 5, 1916. Autopsy. Endothelioma of dura, left middle fossa.*

The patient complained of severe headaches on the left side of the head and face which had been present for a year and were becoming more frequent and more severe.

The general physical examination was negative except for emaciation. The eye-grounds and paranasal sinuses were normal. On neurological examination, there was found paresis of the left abducens, causing an internal strabismus. The left visual field was slightly smaller than the right, and there was interlacing of the color fields. The deep reflexes were slightly increased. The Wassermann test for the blood serum was negative and the spinal

fluid was normal. The urine and blood pressure were normal. There was a slight secondary anæmia.

The patient left the hospital unimproved and came under observation again at the University Hospital on Sept. 8. Her general condition was worse, the headaches were constant, the abducens paralysis was complete. The veins of the left retina were somewhat larger and more tortuous than those of the right. Examination of the other cranial nerves was not altogether satisfactory owing to the patient's lack of coöperation. No other definite abnormalities were discovered and the general examination revealed nothing significant.

On lumbar puncture soon after admission, the cerebrospinal fluid was clear, of a light lemon color, under normal pressure, did not clot, gave negative globulin tests and contained 4 cells per cubic millimeter. The Wassermann test was negative, as it was repeatedly in the blood serum.

A second puncture, one week later, showed a fluid of faint yellowish tinge, clear, with a very faintly positive globulin test. It did not clot. Microscopically there were a few, old crenated red blood cells, but the guaiac reaction was negative.

At a third puncture the fluid was normal.

The patient died on Oct. 5, 1916.

At autopsy, the only significant lesion was a dural endothelioma at the base of the brain in the left middle cranial fossa.

We are indebted to Dr. Gordon Wilson for the privilege of using the records from the University Hospital.

Dr. W. T. Longscope sent us full records of the following case which was observed in his service at the Presbyterian Hospital, New York, and which through his courtesy we report in abstract:

CASE 6.—*B. G., woman, age 43, admitted to the Presbyterian Hospital, N. Y., Feb. 14, 1913. Died March 7, 1913. Autopsy. Arteriosclerosis, chronic diffuse nephritis, arterial hypertension, hemorrhages into the lateral ventricles.*

The history was a typical one for a case of this type. The patient had been treated several times during the preceding 7 years for similar attacks.

Two months before admission she "took cold," had severe headaches, prostration, dyspnœa, anorexia and vomiting. The chief complaint was of headache.

On examination, the patient was a large woman with moderate dyspnoea; slight cyanosis; large, thick-walled peripheral arteries; blood pressure 210 mm. systolic and 140 diastolic; neuroretinitis; urine of small quantity, high specific gravity, a trace of albumin, a few R. B. C., no casts, moderately reduced phthalein. The intense headaches persisted in spite of venesections, hot packs and sodium nitrite.

On Feb. 22, a lumbar puncture with removal of 20 cc. gave much relief from headache.

The fluid was clear, yellow, did not coagulate, gave a positive globulin test and faint blood reaction. The Wassermann was negative. There were 2 cells per cubic millimeter.

On Feb. 26, the spinal fluid was again yellow with a marked blood reaction by the guaiac test but no absorption bands in the spectrum.

After 9 days of comparative comfort, sudden coma occurred with muscular twitching and stertorous breathing, and flaccid paralysis of the left arm and leg.

By phlebotomy, 300 cc. of blood were removed, on which the following chemical determinations were made: urea, 0.020; NaCl, 0.97; sugar, 0.295%. The urine from this period was 140 cc. in quantity and contained 0.6% sugar or 0.84 grams.

Lumbar puncture gave 15 cc. of freshly bloody spinal fluid under some pressure.

Death occurred about 12 hours after the onset of coma.

Autopsy diagnosis: Chronic diffuse nephritis (early arteriosclerotic kidney); cardiac hypertrophy; chronic interstitial myocarditis (early); cerebral hemorrhage into right ventricle, fresh; cerebral hemorrhage into left ventricle, old; pulmonary edema; bronchopneumonia (early); chronic interstitial pancreatitis (focal sclerosis with involvement of Islands of Langerhans); chronic passive congestion of viscera; fibromyoma of uterus; cystic ovary.

In regard to the source of the xanthochromia, we do not consider it necessary to presuppose minute hemorrhages into the meninges and subarachnoid space to explain the coloration of fluids in which no red cells can be found, in which the most delicate chemical tests for hemoglobin derivatives are negative and no bands appear in the spectrum. From the large amounts of globulin and fibrinogen present it is evident that considerable transudation of blood plasma must have occurred; and the normal plasma pigments somewhat concentrated in the thermostat at 37° C. for several days more nearly approach in color the bright yellow of these fluids than do dilute preparations of hemoglobin similarly treated. In our experience, the spinal fluids that definitely contain hemoglobin are somewhat darker, and have rather an amber tint, whereas those giving negative tests for hemoglobin are of a lighter buff yellow color.

Considered from the standpoint of clinical value, all types of yellow spinal fluid are indicative of organic nervous disease, and there are one or two cases on record in which this feature was the determining factor in making that diagnosis. The hemoglobin-containing fluid may conceivably be of value, otherwise, in localizing a cerebral lesion in relation either with the meninges or ventricles. The very general fear of lumbar puncture in cases with signs of brain tumor puts a very definite limitation on the value of spinal fluid examination in general in such cases.

In regard to the Froin compression syndrome we have remarked above that it was of direct importance in enabling us to arrive at the correct diagnosis in our first case. No less an authority than Oppenheim [11] has reported 2 cases in which this finding at lumbar puncture clinched the diagnosis of spinal cord tumor, for which without this finding there was insufficient evidence. "After all," he says, "it is no certain indication of a cord-compressing tumor but it makes this opinion very probable. It has given this diagnosis a firm prop in our cases."

Raven," one of Nonne's pupils, who has made especial study of the possible value of spinal fluid examinations in compression of the cord, accepts this syndrome as evidence of compression and very justly states that it tells nothing concerning the nature or the site of the lesion. Notwithstanding these limitations which must be accepted, a glance at the statistics of published cases shows that of 65 cases in which the diagnosis was confirmed by operation, autopsy, or otherwise beyond doubt, about 70 per cent were cases of tumor of the spinal cord or of the vertebræ. Other lesions less frequently found have been enumerated above.

Of 71 cases, in which mention is made of cellular reaction, there was an increased cell count in 38 and a normal count in 33. It is generally held that the cellular increase indicates

some reaction on the part of the meninges, and many authors offer the cellular content of the fluid as a criterion for the differentiation between tumors (without cells) and adhesive inflammatory processes (with cells). We believe that this factor has no very distinct differential value, as witness Case 2 of our report and the fact that of 51 tumors the cells are reported increased in 17, not increased in 23 and not mentioned in 11.

Of 52 cases, in which the location of the lesion was made clear in the reports, 5 were multiple, 8 cervical, 16 thoracic and 23 lumbar.

Nonne's syndrome, the presence of globulin in large amount without cell increase in the cerebrospinal fluid, apparently has much the same significance as the syndrome of Froin. Perhaps, as Hanes [23] suggests, they are merely different stages of the same process, the xanthochromia appearing late; or, as Nonne [12] believes, they may be variants due to the presence or absence of blood. Against Hanes's view might be cited our third case in which the second specimen obtained at a time when the symptoms of compression were much further advanced was water clear and almost normal. Again Demole [29] reports a case in which during the single puncture the first flow of yellow fluid quickly changed to a normal one. He interpreted this as indicating such a slight grade of obstruction that the release of pressure below the lesion brought about a change of relationships in the canal and permitted the flow of fluid to be re-established.

Nonne's type of fluid is doubtless of more frequent occurrence with compressive lesions than are xanthochromia and coagulation, but it is not entirely beyond suspicion. Isolated globulin increase is occasionally found in other conditions.

SUMMARY.

We have called attention to the clear, yellow spinal fluids occasionally observed at lumbar puncture. Our remarks are based on 5 cases observed and here reported and an analysis of 100 cases from the literature.

The fluids may be divided into two main groups.

1. Those in which the color is due to dissolved hemoglobin or its derivatives, and which as a rule do not coagulate spontaneously and contain only a small amount of globulin. Such fluids usually are associated with brain tumors in contact with the meninges or ventricles.

2. The larger and more important group comprises those cases showing the so-called Froin's syndrome, in which the fluid is transparently clear, yellow, coagulates spontaneously, contains large amounts of globulin, may or may not show pleocytosis, and gives no positive tests for hemoglobin.

This is a "compression syndrome," its main determinants being the isolation of a lumbar cul-de-sac, in which the spinal fluid stagnates, and probably some vascular changes within its walls.

Clinically, with negative X-ray of the vertebral column, it is strongly suggestive of a tumor of the spinal cord, although it may also be associated with intradural inflammatory processes.

REFERENCES.

1. Froin: Inflammations méningées avec réaction chromatique fibrineuse et cytologique du liquide céphalorachidien. Gaz. d. hôp., Par., 1903, 1005.

2. Froin et Foy: Syndrome de coagulation massive au cours d'une méningite. Action nocive d'une infection sous-arachnoïdienne de collargol. Gaz. d. hôp., Par., 1908, Nov. 18.

3. Aubrey: Le syndrome de coagulation massive du liquide céphalorachidien. Thèse de Paris, 1909.

4. Babinski: Méningite hémorragique fibrineuse. Paraplégie spasmodique lombaire; traitement mercuriel; guérison. Soc. méd. d. hôp. de Paris, 1903, Oct. 23, 1083.

5. Cestan et Ravaut: Coagulation en masse et xantochromie du liquide céphalorachidien dans un cas de pachy-méningo-myélite du cone terminal. Gaz. d. hôp., Par., 1904, Sept. 6.

6. Mestrezat: Le liquide céphalo-rachidien. Paris, 1912, p. 425.

7. Schnitzler: Klinische Beiträge zur Kenntnis der mit Muskelatrophien verlaufenden Formen von multipler Sklerose und chronischer Myelitis. Ztschr. f. ges. Neurol. u. Psychiat., Berl., u. Leipz., 1912, XII, Orig., 310.

8. Siemerling: Gliosis spinalis und Syringomyelie. Arch. f. Psychiat. u. Nervenkrankh., Berl., 1913, L, 449.

9. Klieneberger: Ein eigentümlicher Liquorbefund bei Rückmarkstumoren. Monatschr. f. Psychiat. u. Neurol., Berl., 1910, XXVIII, 346.

10. Raven: Weitere Beiträge zur Kenntnis des Kompressionssyndroms im Liquor cerebrospinalis. Deutsche Ztschr. f. Nervenheilk., Leipz., 1913, XLIX, 36.

11. Oppenheim (H.): Ueber Caudatumoren unter dem Bilde der Neuralgia schiadica sive lumbosacralis. Monatschr. f. Psychiat. u. Neurol., Berl., 1914, XXXVI, 391.

12. Nonne: Weitere Erfahrungen zum Kapitel der Diagnose von komprimirenden Rückenmarkstumoren. Deutsche Ztschr. f. Nervenheilk., Leipz., 1913, XLVII, 436.

13. Schlesinger: Ueber erfolgreich operierte Rückenmarkstumoren und über das Kompressionssyndrom des Liquor cerebrospinalis. Wien. klin. Wchnschr., 1915, XXVIII, 463.

14. Cooper: Cerebrospinal Fluid of Anomalous Character in a case of Intraspinal Tumor. Jour. A. M. A., 1910, LV, 2298.

15. Greenfield: On the Value of Quantitative Albumin Estimation of the Cerebrospinal Fluid, with special reference to the syndrome of massive coagulation and xanthochromia. Lancet, Lond., 1912, II, 685.

16. Hartman: Multiple Sarcomatosis of the Brain and Spinal Cord. Texas State J. M., Ft. Worth, 1914, X, 278.

17. Kennedy and Elsberg: A peculiar undescribed disease of the nerves of the cauda equina. Am. Journ. Med. Sc., Phila., 1914, CXLVII, 645.

18. Collins and Elsberg: Giant tumors of the conus and cauda equina. Am. Journ. Med. Sc., Phila., 1914, CXLVII, 493.

19. Mix: Spontaneous massive coagulation of the cerebrospinal fluid with xanthochromia; its significance in the diagnosis of lesions of the spinal cord and its membranes. Surg. Clin., Chicago, 1915, IV, 317.

20. Campbell: Amber color of spinal fluid with coagulation *en masse*. Report of case. Am. Journ. of Surg., 1915, XXIX, 348.

21. Horrax: Studies on the pineal gland. Arch. Int. Med., Chicago, 1916, XVII, 627.

22. Bromer: The syndrome of *coagulation massive et xanthochromie* occurring in a case of tuberculosis of the cervical spine. Am. Journ. Med. Sc., 1916, CLI, 378.

23. Hanes: The spinal fluid syndromes of Nonne and Froin and their diagnostic significance. Am. Journ. Med. Sc., 1916, CLII, 66.

24. Raven: Die Bedeutung der isolierten Eiweissvermehrung und der Xantochromie im Liquor cerebrospinalis für die Diagnose

von Kompression der Rückenmarks. Deutsche Ztschr. f. Nervenheilk., Leipz., 1912, XLIV, 380.

25. Krönig: Histologische und physikalische Lumbalpunctionsbefunde und ihre Deutung. Verhandl. d. Congr. f. inn. Med., 17. Congr., 1899, 565.

26. Mohr: Zur Pathologie des Liquor cerebrospinalis. Deutsche Ztschr. f. Nervenheilk., Leipz., 1912, XLIV, 417.

27. Donath: Beitrag zur Landry'schen Paralyse. Wien. klin. Wchnschr., 1905, XVIII, 1327.

28. Reich: Ueber Gelbfärbung der Cerebrospinalflüssigkeit. Mitt., a. d. Grenzgeb. d. Med. u. Chir., Jena, 1913, XXV, 721.

29. Demole: Syndrome de coagulation massive et de xanthochromie dans un cas de compression médullaire par tumeur rachidienne. Rev. Neurol., 1914-1915, XXII, 648.

MULTIPLE SPONTANEOUS INTRACEREBRAL HEMORRHAGES.

A CONTRIBUTION TO THE PATHOLOGY OF APOPLEXY.

By PHYLLIS GREENACRE,

Resident House Officer, Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital.

(From the Cook County Hospital and the Pathological Laboratory of Rush Medical College.)

Out of 128 cases of intracerebral hemorrhage in 24 (about 18 per cent) the brain showed discrete multiple hemorrhages, none of them being traumatic. The brains were examined because the cause of the coma was in doubt,[1] and trauma had to be excluded. Except two who died on the way to the hospital and four who died in the House of Correction, the patients were all cared for in the Cook County Hospital.

Plurality of hemorrhages, the feature leading to this report, was represented in three brains by three distinct sites of hemorrhage, and in the remaining 21 by two. The combination of one hemorrhage into the internal capsule or basal ganglia and one into the pons was most frequent, occurring in 15 brains (63 per cent). (See diagram of the cerebral circulation, circles *A* and *B*.) Of the seven brains (32 per cent) in which both hemorrhages were into the cerebral hemispheres, five presented bilateral symmetrical hemorrhages implicating both internal capsules or basal ganglia. One brain contained hemorrhages into the cerebrum and the cerebellum, and one hemorrhages into the cerebellum and pons. In one brain only did the pontine hemorrhage appear to be primary, a single large clot in the center of the pons being associated with multiple punctate hemorrhages in the left internal capsule.

The appearance of the pontine lesions varied greatly. In eight brains they were numerous and small, scattered irregularly throughout the pontine substance. In seven brains, moderately large hemorrhages occupied the center of the pons, filling the fourth ventricle and surrounding tissue.

The brain receives its blood supply from two sources, the carotids and the vertebrals which anastomose forming a circle or hexagon at the base of the brain beyond which the arteries are practically terminal. The carotids have a more direct route from the aorta than the vertebrals, being straighter and actually shorter. Further, "the diminution in size," according to Tooth,[2] "is very much more gradual in the vertebral than in the carotid, possibly explaining the lesser liability of the former to atheroma and rupture. The part of the brain requiring the greatest blood supply is the outside. Therefore, the main divisions of the great vessels are distributed over the cortex by gradual dichotomous division comparable to the usual division of arteries throughout the body. Owing to this, hemorrhage is less common in these than in the internal ones. The vessels of internal distribution come off nearly at right angles from the main trunk. This means greater friction. The vessels are small, have a short course, and are practically terminal. Pressure in them is not much less than in the carotids." For these reasons, hemorrhage is more frequent from the branches of the middle cerebrals supplying the internal capsule and basal ganglia than from the other cerebral arteries.

Following any intracranial hemorrhage there is, as in any case of brain compression, a rise in blood pressure and secondarily a slowing of the pulse, due to stimulation of the vasomotor and vagus centers respectively.[3] This means that there is re-established within the arteries a degree of tension in excess of the intracranial tension, which has itself been raised at the time of hemorrhage, owing to the pouring out of blood into a practically closed cavity. The result is an actual increase both in intracranial tension and intra-arterial pressure, which no doubt brings about the rupture of and hemorrhage from other cerebral arteries already weakened by disease. Undoubtedly this is the origin of the hemorrhage from the corresponding branches of the middle cerebral artery of the opposite side occurring in cases of primary internal capsule hemorrhage; the anatomical factors on the two sides are approximately the same; the intra-arterial pressure is actually increased, and the disease of the vessel wall appears as the variable factor. That such changes in blood pressure are not the sole factors determining the production of secondary pontine hemorrhages appears probable in view of the rare occurrence of similar pontine hemorrhages in other conditions of brain compression, as in brain tumor or in extradural hemorrhage, where the mass of extravasated blood may reach

[1] A Consideration of the Relative Frequency of Various Forms of Coma, with Especial Reference to Uremia. Wayne W. Bissell and E. R. LeCount, J. Am. M. Ass., 1915, LXIV, 1041-1045.

[2] Cerebral Hemorrhage. H. H. Tooth. Allbutt and Rolleston's System of Medicine, VIII, 307: Distribution of Encephalic Hemorrhages. S. W. D. Ludlum. J. Nerv. and Ment. Diseases, 1909, XXXVI, 705.

[3] Compression of the Brain. E. von Bergmann in v. Bergmann's System of Medicine. New York, 1904, I, 192: The Blood Pressure Relation of Acute Cerebral Compression, Illustrated by Cases of Intracranial Hemorrhage. H. Cushing. Am. J. Med. Sc., 1903, CXXV, 1017.

a considerable size. Some support for this view was obtained from an examination of the records[1] and charts of five brain tumors with cerebral arteriosclerosis, and of three cases of spontaneous meningeal hemorrhage with arteriosclerosis; in none was there any pontine hemorrhage.

terminal, resembling in these respects the branches of the middle cerebral artery so frequently the site of primary hemorrhage. The generalized increase in blood pressure following deep intracerebral hemorrhage obviously must occur in the intrapontine arteries as well as elsewhere, and continue even

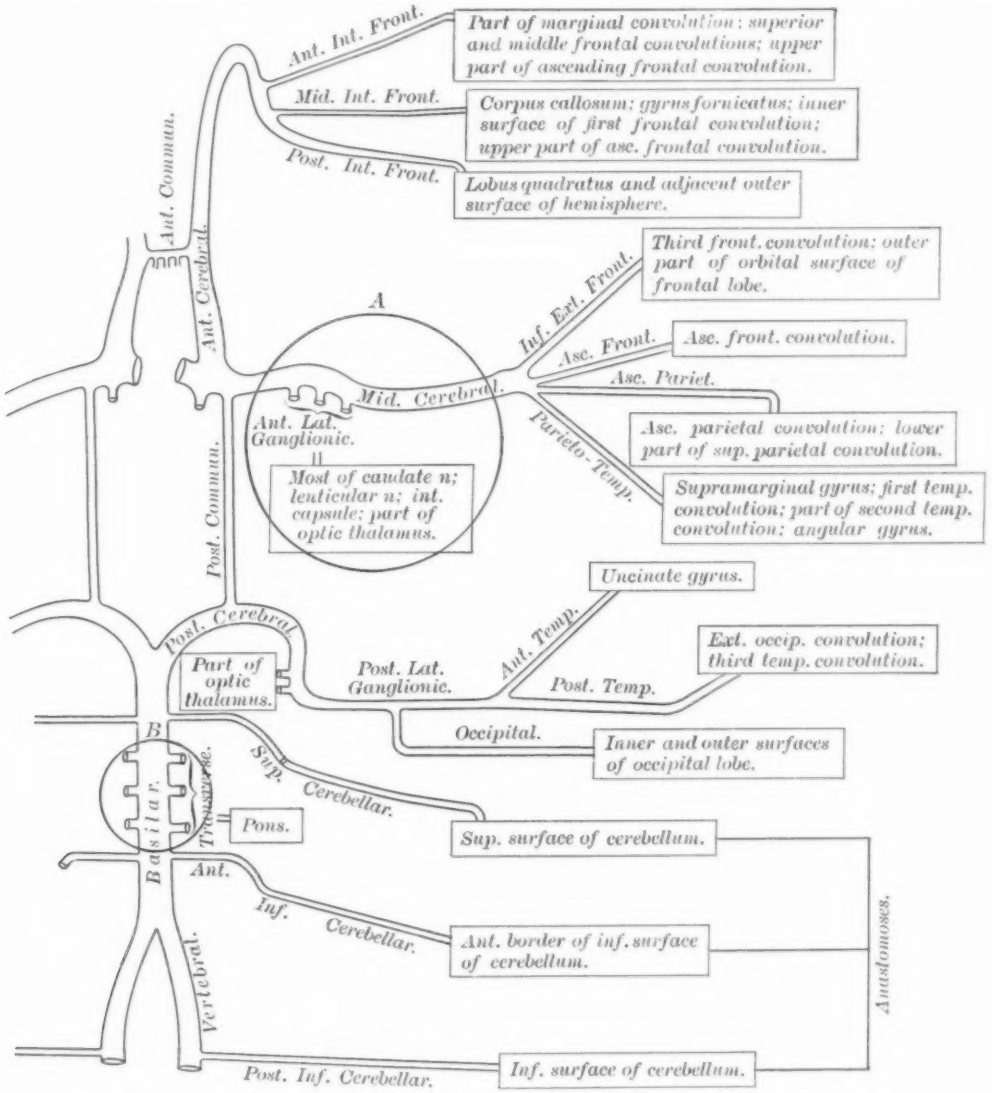
Ant. Int. Front.
Part of marginal convolution; superior and middle frontal convolutions; upper part of ascending frontal convolution.
Mid. Int. Front.
Corpus callosum; gyrus fornicatus; inner surface of first frontal convolution; upper part of asc. frontal convolution.
Post. Int. Front.
Lobus quadratus and adjacent outer surface of hemisphere.
Ant. Commun.
Ant. Cerebral.
A
Third front. convolution; outer part of orbital surface of frontal lobe.
Inf. Ext. Front.
Asc. Front.
Asc. front. convolution.
Asc. Pariet.
Mid. Cerebral.
Ant. Lat. Ganglionic.
Most of caudate n; lenticular n; int. capsule; part of optic thalamus.
Parieto-Temp.
Asc. parietal convolution; lower part of sup. parietal convolution.
Supramarginal gyrus; first temp. convolution; part of second temp. convolution; angular gyrus.
Post. Commun.
Uncinate gyrus.
Post. Cerebral.
Part of optic thalamus.
Post. Lat. Ganglionic.
Ant. Temp.
Ext. occip. convolution; third temp. convolution.
Post. Temp.
B
Occipital.
Inner and outer surfaces of occipital lobe.
Sup. Cerebellar.
Trigeminus.
Basilar.
Pons.
Sup. surface of cerebellum.
Ant.
Inf. Cerebellar.
Ant. border of inf. surface of cerebellum.
Anastomoses.
Vertebral.
Post. Inf. Cerebellar.
Inf. surface of cerebellum.

DIAGRAM OF THE BLOOD SUPPLY OF THE BRAIN, A MODIFICATION OF THAT IN FURSAC AND ROSANOFF'S MANUAL OF PSYCHIATRY (BALTIMORE, 1911, P. 339). THE REGIONS *A* AND *B* ARE THE MOST FREQUENT SITES OF SPONTANEOUS HEMORRHAGE.

Now, as for this most frequent combination, pontine and deep-seated cerebral hemorrhages, it will be remembered that the pontine arteries are branches of the basilar, just before it divides to form the posterior cerebral arteries, the posterior components of the circle of Willis (see diagram of the cerebral circulation). They are short, small branches, given off nearly at right angles from a large trunk, and are practically

after the primary bleeding has been checked by clotting or local pressure or both. When this bleeding has occurred from a branch of the middle cerebral, a lessened amount of blood is sent through this artery and its subdivisions. With the generalized increase in blood pressure referred to, and the absence of any adequate factor of safety to lessen the amount of blood driven with this increased pressure into all the arteries supplying the brain, there is an increased strain in all the other branches of the circle of Willis and perhaps even a back-flow. The site of the greatest strain must be the point of meeting of

[1] Records of post-mortem examinations in the Pathological Laboratory of Rush Medical College.

the back-flow and the normal flow into the posterior cerebrals from the vertebrals by way of the basilar artery, the exact location depending on the comparative length and peripheral friction of the two channel beds, the carotid and the vertebral. Since this meeting takes place in the posterior part of the system owing to the greater length and more circuitous route of the vertebrals, the pressure throughout the basilar is presumably increased above that in the other arteries, and its branches are subjected to unusual strain. It is probable that the pontine arteries suffer more frequently than the cerebellar, since the latter are safeguarded in some measure by their anastomoses, their greater length and their somewhat greater size. This point might, in future material, be put to a further test by comparing the cases showing ample connecting branches of the circle of Willis and those with narrow or obliterated connectives.

Several reports of multiple spontaneous cerebral hemorrhages have been published.[5] Most of them are descriptions of single brains containing numerous hemorrhages (2-28), considered chiefly as interesting curiosities.

In the only article which I have so far been able to find, dealing at all comprehensively with multiple spontaneous hemorrhages,[6] they are described in a general review of 67 cases of pontine hemorrhage, and the issues are confused by failure of the author to differentiate clearly between spontaneous and traumatic hemorrhages. Spontaneous secondary pontine hemorrhages are due, according to Dr. Attwater, "to a general increase in cerebral blood pressure following primary capsular hemorrhages, associated with a degenerate condition of the blood vessels." In support of this explanation he offers a single case of pontine hemorrhage with extradural hemorrhage and skull fracture, ignoring the probable rôle of the obvious trauma in the production of the pontine lesion. Traumatic pontine hemorrhage, on the other hand, is produced, in his opinion, "by a local disturbance of blood pressure in the neighborhood of the pons, due to the movement of the brain and intracranial contents backward and downward toward the foramen magnum, at the moment of impact"; a theory strikingly at variance with the generally accepted view that these hemorrhages are essentially the result of contusions produced by the transmission of a force which is usually sufficient to fracture the base of the skull.[7] The untenability of any theory of traumatic hemorrhage by local increase in blood pressure, is apparent in view of the great pressure (4-11 atmospheres, or 16-44 times the normal pressure),[8] necessary to rupture a normal blood vessel.

Records of 15 cases of traumatic pontine hemorrhages were examined for the purposes of comparison. Twelve of the 15 (80 per cent) occurred with basal skull fracture of the posterior and middle fossæ. In only four (28 per cent) was there a degree of arteriosclerosis sufficient to be detected grossly, in contrast to 67 per cent of the group of secondary spontaneous pontine hemorrhages. The difference in appearance between the two groups is best shown by the diagrams of representative cases (Figs. 1 and 2). The traumatic hemorrhages are almost uniformly punctate, frequently grouped around the periphery of the pons, and connected with small subpial extravasations and numerous lacerations, whereas the spontaneous pontine hemorrhages are remarkably free from such obvious contusions. These differences are frequently of great medico-legal importance.

CONCLUSION.

In the examination of an adequate number of brains containing multiple spontaneous hemorrhages, pontine hemorrhage was found secondary to extensive hemorrhage into the internal capsule and basal ganglia in a majority of cases. The liability of the pontine arteries to secondary rupture is due probably to their anatomic peculiarities (in that they are short, small, terminal branches given off nearly at right angles from a large trunk), and possibly to a disturbance of blood pressure in the circle of Willis with a back-flow into the posterior branches.

EXPLANATION OF PLATE.

FIG. 1.—*Traumatic Intrapontine Hemorrhages.*—A man, aged 50, was brought to the hospital in coma after being struck by an automobile. He died an hour later without regaining consciousness.

Anatomic Findings: Traumatic fracture of skull, 20.9 cm. in length, beginning in the right temple at the line of the suture, going down into the middle of the middle fossa to the right optic foramen, and then passing across to the posterior plate of the ethmoid bone; lacerations and contusions of both temporal lobes; subdural and intraleptomeningeal hemorrhage (wt. 20 gm.) in both middle fossæ; numerous punctate hemorrhages in the pons; traumatic hemorrhages into the pericranial tissues; contusions and lacerations of the face, left forearm and left popliteal space. (This chart and that for Fig. 2 were made by sketching with a paraffin pencil the outlines on glass laid on the brain segments.)

FIG. 2.—*Spontaneous Secondary Intrapontine Hemorrhage.*—A man, aged 60, was on his way to Cook County Hospital for treatment when he suddenly became unconscious on the car. He died within 30 minutes after reaching the hospital, without regaining consciousness.

Anatomic Findings: Spontaneous intracerebral hemorrhage into the right internal capsule and basal ganglia (greatest dimensions 10.5 cm. anteroposteriorly; 6 cm. laterally; 5 cm. from above downward); intrapontine hemorrhage (2.5 cm. x 1.5 cm.—greatest diameters); slight hyperemia of the leptomeninges; marked sclerosis of the basilar artery; fibrous external pachymeningitis.

[5] 1. Sur un cerveau polyhémorragique. Anglade: J. de méd. de Bordeaux, 1908, XXXVIII, 570. 2. Hémorragie cérébrale récente à foyers multiples. A. Souques, N. iconog. de la Salpêtrière, 1911, XXIV, 193. 3. Double Cerebral Hemorrhage in a Young Man. A. J. Shinnie, Brit. M. J., 1912, II, 780. 4. Hémorragies étendues et multiples des hémisphères cérébraux et du corps calleux. P. Lereboullet, Bull. and Mém. Soc. méd. des hôp. de Paris, 1910, XXX, 534. 5. A Brain with Three Subsequent Hemorrhages. L. Freyburger. Tr. Path. Soc. Lond., 1897, XLIX, 36. 6. Cerveau polyhémorragique. Robert Lafarge, J. de méd. de Bordeaux, 1910, XL, 420.

[6] Pontine Hemorrhages. H. L. Attwater, Guy's Hosp. Rep., 1911, LXV, 339.

[7] Ueber Hirnverletzungen durch stumpfe Gewalt und ihre Beziehungen. O. Tillman, Arch. f. Klin. Chir., 1902, LXVI, 750; Etudes expérimentales et cliniques sur les traumatismes cérébraux. H. Duret, Paris, 1878, 39.

[8] The Blood Flow. Tigerstedt and Murlin. A Text-Book of Human Physiology. New York, 1906, p. 198.

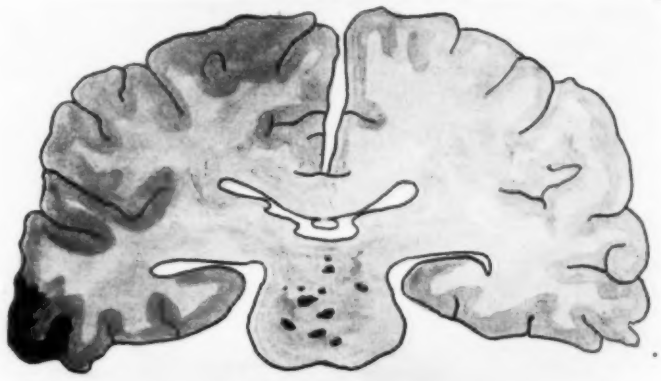

FIG. 1.

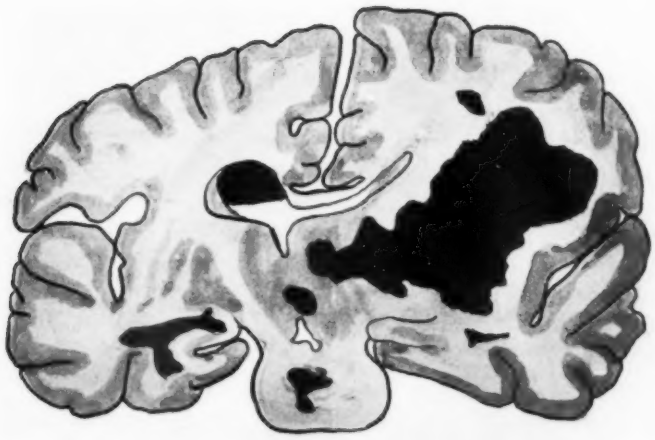

FIG. 2.

TITLES OF PAPERS APPEARING DURING THE YEAR, ELSEWHERE THAN IN THE BULLETIN, BY PRESENT AND FORMER MEMBERS OF THE HOSPITAL AND MEDICAL SCHOOL STAFF.

AUER, J.
The action of the depressor nerve on the pupil.—*Am. J. Physiol.*, 1916, xi, 143; also *Proc. Soc. Exper. Biol. & Med.*, 1915-16, xiii, 52.

AUER, J., and GATES, F. L.
The absorption of adrenalin after intratracheal injection.—*J. Exper. M.*, 1916, xxiii, 757; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 315.

AUER, J., and MELTZER, S. J.
The intravenous injection of magnesium sulphate for anesthesia in animals.—*J. Exper. M.*, 1916, xxiii, 641; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 287.
The influence of intravenous injections of magnesium sulphate upon the activities of deglutition.—[Abstr.] *Proc. Soc. Exper. Biol. & Med.*, 1916, xiii, 106.

AUSTRIAN, C. R.
Summer diarrhea and vomiting of childhood.—*Bull. Med. & Chir. Fac. Maryland*, 1916-17, ix, 72.

AUSTRIAN, C. R., and BLOOMFIELD, A. L.
Observations on the typhoidin reaction.—*Arch. Int. Med.*, 1916, xvii, 663.

BAETJER, F. H.
Visceroptosis from the radiographer's viewpoint.—*Am. J. Orthop. Surg.*, 1916, xiv, 530.
Pulmonary tuberculosis from a rœntgenological standpoint.—*Internat. Clin.*, 1916, 26, s. iii, 124.
The early diagnosis of pulmonary tuberculosis by X-rays. The rœntgenological aspect.—*Nat. Ass. Study & Prev. Tuberc. Tr.*, 1916, xii, 150.

BAETJER, W. A., BARKER, L. F., and MILLER, S. R.
The clinical diagnosis of acute leukemic states.—*South. M. J.*, 1916, ix, 107.

BARKER, L. F.
The clinical diagnosis of internal diseases.—N. Y. & Lond., 1916, D. Appleton & Co. 1025; 1063; 1039. p. 8°. Vol. ii-iv. Monographic Medicine.
On the growth of medical knowledge concerning the malady known as infantile paralysis, acute anterior poliomyelitis, or the Heine-Medin disease.—*Charlotte (N. C.) M. J.*, 1916, lxxiv, 257.
Relation of the preclinical laboratory courses to the work of the clinical years.—*J. Am. M. Ass.*, 1916, lxvi, 631.
War and the nervous system.—*J. Nerv. & Ment. Dis.*, 1916, xliv, 1.
Development of science of diagnosis.—*J. South. Car. M. Ass.*, 1916, xii, 278.
Syphilis and internal medicine.—*N. York M. J.* [etc.,] 1916, cili, 385.
The teaching of clinical medicine. —*Science*, 1916, n. s., xliii, 799; also *Proc. Ass. Am. M. Coll.*, 1916, 43.

BARKER, L. F., BAETJER, W. A., and MILLER, S. R.
The clinical diagnosis of acute leukemic states.—*South. M. J.*, 1916, ix, 107.

BARKER, L. F., and SMITH, F. J.
Functional renal tests (phenolsulphonephthalein; lactose) in orthostatic albuminuria.—*Am. J. M. Sc.*, 1916, cli, 44.

BAYNE-JONES, S.
Eventration of the diaphragm, with report of a case of right-sided eventration.—*Arch Int. Med.*, 1916, xvii, 221.

BEALL, K. H.
Pellagra in Texas.—*South. M. J.*, 1916, ix, 20.
Pellagra.—*Texas State J. M.*, 1916, xii, 170.

BERKLEY, H. J.
The defective delinquent.—*Maryland Psychiat. Q.*, 1915-16, v.
Mental diseases, etiology.—*Ref. Handb. Med. Sc.*, N. Y., 3d ed., 1916, vi, 392.

BERNHEIM, B. M.
Saphenoperitoneal anastomosis for ascites.—*Am. J. M. Sc.*, 1916, cli, 806.
Choice of operation in the cure of aneurysms of the extremity.—*Interstate M. J.*, 1916, xxiii, 326.

BERNHEIM, B. M., KING, J. H., and JONES, A. T.
The effect of removal of the spleen upon blood transfusion.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 10.

BERRY, J. McW.
Orthopedic surgery for nurses.—Phila. & Lond., 1916, W. B. Saunders Co. 97 p. 8°.
Observations on the presence of rœntgenological shadows associated with subdeltoid bursitis; also on the presence of similar shadows in other parts of the body.—*Am. J. Orthop. Surg.*, 1916, xiv, 476.
Retarded ossification as an etiologic factor in traumatic arthritis and epiphysitis.—*J. Am. M. Ass.*, 1916, lxvi, 868.

BLACKFAN, K. D.
Cutaneous reaction from proteins in eczema.—*Am. J. Dis. Child.*, 1916, xi, 441.

BLOCK, E. B.
The relation of the mammary glands to nervousness and menstruation.—*J. Med. Ass. Georgia*, 1915-16, v, 155.

BLOCK, E. B., and NYUN, K.
The importance of counting pus cells in the urine.—*South. M. J.*, 1916, ix, 972.

BLOODGOOD, J. C.
Cancer of the breast; figures which show that education can increase the number of cures.—*J. Am. M. Ass.*, 1916, lxvi, 552.
First aid in accidental wounds.—*Ibid.*, 1916, lxvi, 758.
First aid instruction to police force of Baltimore City.—*Maryland M. J.*, 1916, lix, 34.
American First Aid Conference.—*Ibid.*, 1916, lix, 45.
The objects of the First Aid Conference.—*Mil. Surgeon*, 1916, xxviii, 44; also *Wisconsin M. J.*, 1915-16, xiv, 395.
Control of cancer.—*Pub. Health. Mich.*, 1916, iv, 285.
Primary treatment of accidental wounds.—*South. M. J.*, 1916, ix, 644.
First aid to the injured. A survey of the present experience and prevailing opinion as to the treatment of accidental wounds immediately after the injury.—*Surg., Gynec. & Obst.*, 1916, xxii, 121.
Gas-bacillus infection; surgical bacteriology.—*Ibid.*, 1916, xxiii, 182; also *Tr. Am. Surg. Ass.*, xxxiv, 122.
Cancer investigations.—*Virginia M. Semi-Month.*, 1916, xx, 497.
What every woman should know about cancer of the breast.—*Prevention of Cancer Series.* Pamphlet No. viii, issued by the Council on Health and Public Instruction of Am. M. Ass.

BLOOMFIELD, A. L., and AUSTRIAN, C. R.
Observations on the typhoidin reaction.—*Arch. Int. Med.*, 1916, xvii, 663.

BLUMER, G.
The modern medical school: its relations to the hospital and to the medical profession.—*Albany M. Ann.*, 1916, xxxvii, 493.
A note on the simulation of diabetes mellitus.—*Boston M. & S. J.*, 1916, clxxiv, 48.
What attitude should the physician take towards health insurance?—*Penn. M. J.*, 1916, xix, 756.
Importance of anaphylaxis in clinical medicine.—*Providence M. J.*, 1916, xvii, 135.

BLUMER, G., PEPPER, W., and WOOLLEY, P. G.
The function of the dispensary.—*J. Am. M. Ass.*, 1916, lxvi, 1156; also *Proc. Ass. Am. M. Coll.*, 1916, 99.

BOGGS, T. R., and PINCOFFS, M. C.
A case of pulmonary moniliasis in the United States.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 62.

BOGGS, T. R., and WINTERNITZ, M. C.
Acute suppurative hypophysitis as a complication of purulent sphenoidal sinusitis.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 56.

BREM, W. V.
Blood transfusion, with special reference to group tests.—*J. Am. M. Ass.*, 1916, lxvii, 190.

BRIDGMAN, E. W., and SCHMEISSER, H. C.
Heart block caused by gumma of the septum.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 90.

BROWN, HELEN W.
A literary forerunner of Freud.—*Psycho-analyt. Rev.*, 1916, iii.

BROWN, T. R.
Clinical investigations on intestinal auto-intoxication, especially as regards the question of specificity of toxin.—*Am. J. M. Sc.*, 1916, cli, 845.
A clinical study of the secretions of the digestive tract.—*Boston M. & S. J.*, 1916, clxxv, 775.
Border-line problems in digestive pathology involving both medical and surgical treatment.—*South. M. J.*, 1916, ix, 867.

BROWN, T. R., and FREEMAN, E. B.
The effect of variations of the gastric secretion upon the composition of the saliva.—*Maryland M. J.*, 1916, lix, 176.

BUNTING, C. H., and YATES, J. L.
Bacteriological results in chronic leukemia and in pseudoleukemia.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1916, xxiv, 123.

BURNAM, C. F., and KELLY, H. A.
A résumé of results in the radium treatment of 347 cases of cancer of the uterus and vagina.—*Am. J. Obst.*, 1916, lxxiv, 326.

BURNS, J. E.
The use of thorium in urology and rœntgenology.—*Am. J. Rœntgenol.*, 1916, iii, 482.

BURROW, T.
Permutations within sphere of consciousness.—*J. Abnorm. Psychol.*, 1916-17, xi, 178.
The philology of hysteria: an *a priori* study of the neuroses in the light of Freudian psychology.—*J. Am. M. Ass.*, 1916, lxvi, 783.

BURROWS, M. T.
The functional relation of intercellular substances in the body to certain structures in the egg cell and unicellular organisms.—[Abstr.] *Anat. Rec.*, 1916, x, 189.

BYRNES, C. M.
A clinical and pathological study of a condition occurring in the aged usually attributed to cerebral arteriosclerosis.—*J. Nerv. & Ment. Dis.*, 1916, xliii, 489.

CAMERON, D. F.
Variations in renal function dependent on surgical procedures.—*J. Am. M. Ass.*, 1916, lxvi, 1765.

CAMPBELL, C. M.
The neurotic child; some familiar symptoms and their problems.—*Am. J. Dis. Child.*, 1916, xii, 425.
The relation of social and economic factors to mental hygiene.—*Am. J. Pub. Health*, 1916, vi, 1278.
Constitutional inferiority.—*Maryland Psychiat. Q.*, 1916, vi.
The nature of the dementia in dementia paralytica.—*Psychiat. Bull.*, 1916, ix, 316.

CARTER, D. W., JR.
Hematochyluria; observations on the fat content of the urine and the pathology of the condition.—*Arch. Int. Med.*, 1916, xviii, 541.

CARTER, E. P.
The simple interpretation of polygraphic tracings.—*J. Lab. & Clin. M.*, 1916, i, 719.

CAULK, J. R.
The diagnosis of renal infections—An analytic study of 182 cases.—*Lancet-Clinic*, 1916, cxv, 99.

CAULK, J. R., and GREDITZER, H. G.
Observations on the bladder in diseases of the central nervous system. Report of 50 cases.—*Interstate M. J.*, 1916, xxiii, 36.
Medical and surgical progress. The verumontanum and its diseases. A review of recent literature.—*Ibid.*, 1916, xxiii, 139.
The efficiency of dispensary treatment in chronic infections of the prostate and seminal vesicles.—*Ibid.*, 1916, xxiii, 702.

CHESNEY, A. M.
The latent period in the growth of bacteria.—*J. Exper. M.*, 1916, xxiv, 387.

CHURCHMAN, J. W.
The diagnosis of genito-urinary tuberculosis.—*Med. Rec.*, 1916, lxxxix, 511.

CLARK, A. H.
The interrelation of the surviving heart and pancreas of the dog in sugar metabolism.—*J. Exper. M.*, 1916, xxiv, 621.

CLARK, J. G.
Results obtained by the use of radium in the treatment of cancer of the uterus.—*Ann. Surg.*, 1916, lxiv, 602.
Phases of the cancer problem.—*J. Med. Soc. N. Jersey*, 1916, xiii, 461.
Final results in 12 cases of colectomy.—*Surg., Gynec. & Obst.*, 1916, xxii, 533.
The treatment of cancer of the uterus.—*Tr. Am. Gynec. Soc.*, 1916, xli, 504.

COLSTON, J. A. C.
Impressions of a year in a French base hospital.—*Johns Hopkins Alumni Mag.*, 1916, iv, 189.
Personal experiences at the Red Cross hospitals at Pau, France.—*Maryland M. J.*, 1916, xlix, 14.

COLSTON, J. A. C., and GORTON, W. S.
The radiographic efficiency of the Coolidge X-ray tube.—*Am. J. Roentgenol.*, 1915-16, n. s., iii, 388.

COOK, H. W.
Peptic ulcer from the point of view of medical selection.—*Med. Rec.*, 1916, lxxxix, 148.
What life insurance companies can do to assist in the control of cancer.—*Ibid.*, 1916, lxxxix, 863.
The obligation of the medical examiner.—*Texas State J. M.*, 1916, xi, 633.

CORNER, G. W.
Mithridatium and theriac. The most famous remedies of old medicine.—*University of California Chronicle*, 1916.

CULLEN, T. S.
Embryology, anatomy, and diseases of the umbilicus, together with diseases of the urachus.—Phila., 1916, W. B. Saunders Co. 701 p. 4°.
The relation of obstetrics, gynecology and abdominal surgery to the public welfare.—*J. Am. M. Ass.*, 1916, lxvi, 239.
Adenomyoma of the rectovaginal septum.—*Ibid.*, 1916, lxvii, 401.
Early tuberculosis of the cervix.—*Surg., Gynec. & Obst.*, 1916, xxii, 261.
Adenomyoma of the round ligament and incarcerated omentum in an inguinal hernia, together forming one tumor.—*Ibid.*, 1916, xxii, 258.
The cancer campaign and what it has accomplished—*Virginia M. Semi-Month.*, 1916, xx, 516.

CUSHING, H.
Headache.—[Abstr.] *Boston M. & S. J.*, 1916, clxxiv, 325.
Hereditary anchylosis of the proximal phalangeal joints (symphalangism.—*Genetics*, 1916, i, 90.
On convulsive spasm of the face produced by cerebellopontine tumors.—*J. Nerv. & Ment. Dis.*, 1916, xliv, 312.
Anosmia and sellar distension as misleading signs in the localization of a cerebral tumor.—*Ibid.*, 1916, xliv, 415.
Concerning operations for the cranio-cerebral wounds of modern warfare.—*Mil. Surgeon*, 1916, xxxviii, 601; xxxix, 22.
Yale in medicine.—In The Book of the Yale Pageant, New Haven, 1916. Yale Univ. Press.
With the British medical corps in France.—*Yale Rev.*, 1916, v, 523.

CUSHING, H., and HORRAX, G.
The presence of posterior lobe secretion in the cerebrospinal fluid.—*Proc. Am. Soc. Biol. Chemists*, 1916, p. xxxvii.

CUSHING, H., and WALKER, C. B.
Studies of optic nerve atrophy in association with chiasmal lesions.—*Arch. Ophth.*, 1916, xlv, 407.

DAVIS, D. M., and MARSHALL, E. K., JR.
The influence of the adrenals on the kidney.—*J. Pharmacol. & Exper. Therap.*, 1916, viii, 525; also *Proc. Am. Soc. Biol. Chemists*, 1916, p. xxxvii.

DAVIS, E. G.
Vesical drainage; historical review and presentation of a new apparatus.—*J. Am. M. Ass.*, 1916, lxvi, 1680.

DAVIS, J. S.
Partial epiphysial transplantation for defect in fibula. Report of case under observation over five years.—*Ann. Surg.*, 1916, lxiv, 519.
Plastic and reconstructive surgery.—*J. Am. M. Ass.*, 1916, lxvii, 338.

DICK, GLADYS R., and DICK, G. F.
Immune reactions in scarlet fever. II. Antigenic properties of bacteria found in scarlatina.—*J. Infect. Dis.*, 1916, xix, 638.

DICK, GLADYS R., DICK, G. F., and RAPPAPORT, B.
A leptothrix associated with chronic hemorrhage nephritis.—*J. Infect. Dis.*, 1916, xviii, 216.

DUFFY, R. N.
The necessity of cystoscopic examinations in the diagnosis of urological lesions; illustrative cases.—*Charlotte (N. C.) M. J.*, 1916, lxxiv, 60.

DUNTON, W. R., JR., and SARGENT, G. F.
Duration of paresis following treatment.—*Am. J. Insan.*, 1916, lxxiii, 241.
Christmas at the Sheppard and Enoch Pratt Hospital.—*Maryland Psychiat. Q.*, 1915-16, v, 70.

ELMENDORF, M. F., and WALKER, J. E.
Hookworm history schedules of two male patients treated with oil of chenopodium at the U. S. Marine Hospital, Wilmington, N. C.—*Virginia M. Semi-Month.*, 1915-16, xx, 552.

EMERSON, C. P.
The mold infections of the lung.—*Indianapolis M. J.*, 1916, xix, 1.
Modern conception of one form of nephritis.—*J. Indiana M. Ass.*, 1916, ix, 105.

EMMONS, A. B.
The profession of medicine; a collection of letters from graduates of the Harvard Medical School.—Cambridge, Mass., 1916, Harvard University Press, 114 p. 8°. Also *Harvard Grad. Mag.*, 1916, xxiv, 477.
Industrial medical supervision.—*Boston M. & S. J.*, 1916, clxxiv, 495.

ERLANGER, J.
Studies in blood pressure estimations by indirect methods. I. The mechanism of the oscillatory criteria.—*Am. J. Physiol.*, 1915-16, xxxix, 401.
Studies in blood pressure estimation by indirect methods. II. The mechanism of the compression sounds of Korotkoff.—*Ibid.*, 1916, xl, 82.
A note on the contractility of the musculature of the auriculo-ventricular valves.—*Ibid.*, 1916, xl, 150.

ESTES, W. L.
Fractures of the femur.—*Ann. Surg.*, 1916, lxiv, 74.

EVANS, F. A.
Observations on the origin and status of the so-called "transitional" white blood cell.—*Arch. Int. Med.*, 1916, xvii, 1.
Experimental study of the mononuclear cells of the blood and tissues. With special reference to the so-called transitional cell.—*Ibid.*, 1916, xviii, 692.
The cytology of the exudate in the early stages of experimental pneumonia.—*J. Infect. Dis.*, 1916, xix, 441; also *Proc. Soc. Exper. Biol. & Med.*, 1916, xiii, 99. [Abstr.]
The practical significance of the oxidase reaction as applied to blood cells.—*Proc. N. York Path. Soc.*, 1916, xv, 143.
Gaucher's splenomegaly in a child.—*Ibid.*, n. s. xvi.

EVANS, H. M.
On the behavior of the ovary and especially of the atretic follicle towards vital stains of the azo group.—[Abstr.] *Anat. Rec.*, 1916, x, 264; also *Proc. Soc. Exper. Biol. & Med.*, 1916, xiii, 80.

FELTON, L. D.
Hydrotherapy as applied to psychiatric patients.—*Maryland Psychiat. Q.*, 1915-16, v, 33.

FISHBAUGH, E. C.
Fractional determination of gastric secretions.—*J. Am. M. Ass.*, 1916, lxvii, 1275.

FISHER, A. L.
Torticollis—a review.—*Am. J. Orthop. Surg.*, 1916, xiv, 669.

FLEXNER, S.
What we know about the transmission of infantile paralysis.—*Am. J. Obst.*, 1916, lxxiv, 338.
A note on the serum treatment of poliomyelitis (infantile paralysis).—*J. Am. M. Ass.*, 1916, lxvii, 583; also *Science*, 1916, n. s., xliv, 259.
The rapid production of antidysenteric and antimeningococcic sera.—*J. State Med.*, 1916, xxiv, 161; 193.
The nature, manner of conveyance and means of prevention of infantile paralysis.—*J. Am. M. Ass.*, 1916, lxvii, 279; also *Arch. Pediat.*, 1916, xxxiii, 562; *Med. Times*, 1916, xliv, 239; *Pediatrics*, 1916, xxvii, 341; *Science*, 1916, n. s., xliv, 73; *Wisconsin M. J.*, 1916, xv, 84; *N. York M. J.* [etc.], 1916, civ, 168.

FLEXNER, S., and AMOSS, H. L.
Chemical versus serum treatment of epidemic meningitis.—*J. Exper. M.*, 1916, xxiii, 683; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 239.

FLINT, J. M.
The treatment of fractures by methods of suspension and extension.—*Ann. Surg.*, 1916, lxiii, 641.
Localization and extraction of projectiles and shell fragments.—*Ann. Surg.*, 1916, lxiv, 151; also *Tr. Am. Surg. Ass.*, 1916, xxxiv, 26.
The four-post fracture bedstead.—*Ann. Surg.*, 1916, lxiv, 613.
The organization and problems of a war hospital.—*Mil. Surgeon*, 1916, xxxviii, 405.
Simple mechanotherapeutic apparatus for military hospitals.—*Surg., Gynec. & Obst.*, 1916, xxiii, 228.

FLOURNOY, H.
Paralysie générale chez une oxycéphalique.—*N. iconog. de la Salpêtrière*, 1916, xxviii, 15.

FORD, W. W.
Studies on aerobic spore-bearing non-pathogenic bacteria. Part I. Introduction.—*J. Bact.*, 1916, i, 273.
Studies on spore-bearing non-pathogenic bacteria. Part II. Miscellaneous cultures. Classification.—*Ibid.*, 1916, i, 518; 527.

FORD, W. W., and LAWRENCE, J. S.
Studies on spore-bearing non-pathogenic bacteria. Part I. Spore-bearing bacteria in milk.—*J. Bact.*, i, 277.

FOWLER, H. A.
Remarks on the diagnosis of renal and ureteral calculi.—*Maryland M. J.*, 1916, lix, 183.
Renorenal reflex pain; report of a case.—*Surg., Gynec. & Obst.*, 1916, xxii, 454.

GARBER, J. R.
Significance of the ammonia co-efficient in obstetrical work.—*South. M. J.*, 1916, ix, 900.

GATCH, W. D.
Instruction of medical students and hospital internes in anesthesia.—*Am. J. Surg.*, 1916, xxx, 98.
Thoracoplasty for chronic empyema.—*J. Indiana M. Ass.*, 1916, ix, 190.

GERAGHTY, J. T.
Treatment of bladder tumors.—*New York M. J.* [etc.] 1916, civ, 838.

GIFFIN, H. Z.
The treatment by splenectomy of splenomegaly with anemia associated with syphilis.—*Am. J. M. Sc.*, 1916, cli, 5.

GILCHRIST, T. C.
Cancer of the skin.—*Hosp. Bull. Univ. Maryland*, 1915-16, xi, 181.

GILCHRIST, T. C., and KETRON, L. W.
Report of two cases of idiopathic hemorrhagic sarcoma (Kaposi), one presenting unusual features, with special methods of treatment and investigation.—*J. Cutan. Dis. incl. Syph.*, 1916, xxxiv, 429.
A unique case of atrophy of the fatty layer of the skin, preceded by the ingestion of the fat by large phagocytic cells—macrophages.—*J. Cutan. Dis. incl. Syph.*, 1916, xxxiv, 728.

GILMAN, P. K.
Dermoid tumors of the mouth.—*Surg., Gynec. & Obst.*, 1916, xxii, 672.

GIRDWOOD, J.
The thermometer in the diagnosis of active pulmonary tuberculosis.—*Bull. Med. & Chir. Fac. Maryland*, 1916-17, ix, 74.

GOLDSBOROUGH, F. C.
Toxemias in pregnancy.—*J. Mich. M. Soc.*, 1916, xv, 328.

GOODPASTURE, E. W.
Tumors in relation to senescence in dogs.—*J. Cancer Research*, 1916, i, 363.
Double primary abdominal pregnancy.—*J. Med. Research*, 1916, xxxiv, 359.

GOODPASTURE, E. W., and CLARK, G.
A study of a toxic substance of the pancreas.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 1.

GOODPASTURE, E. W., and WISLOCKI, G. B.
Old age in relation to cell-overgrowth and cancer.—*J. Med. Research*, 1915-16, xxxiii, 455; also *Johns Hopkins Hosp. Rep.*, 1916, xviii, 4. [Abstr.]

GORHAM, L. W.
Address to the graduating class of the Glens Falls Hospital Training School for Nurses, October 10, 1916.—*Albany M. Ann.*, 1916, xxxvii, 518.

GORTON, W. S., and COLSTON, J. A. C.
The radiographic efficiency of the Coolidge X-ray tube.—*Am. J. Roentgenol.*, 1915-16, n. s., iii, 388.

GREY, E. G.
Studies on the localization of cerebellar tumors: ii. The pointing reaction and the caloric test.—*Am. J. M. Sc.*, 1916, cli, 693.
An experimental study of the effect of cholecystgastrostomy on gastric acidity.—*J. Exper. M.*, 1916, xxiii, 15.
Studies on the localization of cerebellar tumors, the position of the head and suboccipital discomforts.—*Ann. Surg.*, 1916, lxiii, 129.
On localization of function in the canine cerebellum.—*J. Nerv. & Ment. Dis.*, 1916, xliii, 105.

GRIFFITH, F. W.
The sterile woman.—*South. M. J.*, 1916, ix, 153.

GUNDRUM, F. F., and GRAZER, F
A study in handicaps.—*Calif. State J. M.*, 1916, xiv, 99.

GWYN, N. B.
Acute yellow atrophy of the liver.—*Ref. Handb. Med. Sc., N. Y.* 3d ed., 1916, vi, 40.
Hyperemia of the liver.—*Ibid.*, 1916, vi, 59.

HALSTED, W. S.
An experimental study of circumscribed dilation of an artery immediately distal to a partially occluding band, and its bearing on the dilation of the subclavian artery observed in certain cases of cervical rib.—*J. Exper. M.*, 1916, xxiv, 271.
As to the cause of the dilatation of the subclavian artery observed in some cases of cervical rib: a clinical and experimental study.—*Tr. Am. Surg. Ass.*, 1916, xxxiv, 273.

HAMMAN, L.
Spontaneous pneumothorax.—*Am. J. M. Sc.*, 1916, cli, 229.

HAMMAN, L., and WOLMAN, S.
Chronic non-tuberculous pulmonary infections.—*Nat. Ass. Study & Prev. Tuberc. Tr.*, 1916, xii, 171.

HANES, F. M.
The spinal-fluid syndromes of Nonne and Froin and their diagnostic significance.—*Am. J. M. Sc.*, 1916, cliii, 66.
An experimental study of the intraspinous method of therapy in syphilis of the nervous system.—*Old Dominion J. M. & S.*, 1916, xxii, 12.
Recent advances in the diagnosis and specific treatment of lobar pneumonia.—*Virginia M. Semi-Month.*, 1915-16, xx, 503.

HANES, F. M., and WILLIS, A. M.
Circumscribed cysts of the leptomeninges, with the report of a successful operative case.—*Am. J. M. Sc.*, 1916, cliii, 859.

HARRIS, N. MACL.
Milk-sickness.—*Ref. Handb. Med. Sc., N. Y.*, 3d ed., 1916, vi, 522.

HASTINGS, T. W.
Discussion on immunization and its practical applications.—*Tr. Cong. Am. Phys. & Surg.*, 1916, x.

HENDERSON, D. K.
The treatment of drug addiction.—*Glasgow M. J.*, 1916, lxxxv, 190.

HENNINGTON, C. W.
Application of the so-called new war-time antiseptics to the several branches of surgery of civil life.—*Buffalo M. J.*, 1916, lxxii, 163.

HEUER, G. J.
The cerebral nerve disturbances in exophthalmic goitre.—*Am. J. M. Sc.*, 1916, cli, 339.

HIGGINS, W. H.
Medical co-operation in the study of mental efficiency.—*Virginia M. Semi-Month.*, 1916, xxi, 29.

HIRSCHFELDER, A. D.
Studies on the effects of acids.—*J. Am. M. Ass.*, 1916, lxvii, 1891.
Brain lipoid as a hemostatic.—*Science*, 1916, n. s. xliv, 251.

HIRSCHFELDER, A. D., and SCHULTZ, F. W.
Experiences with ethylhydrocuprein in the treatment of measles, scarlet fever and other infections.—*Am. J. Dis. Child.*, 1916, xi, 361.

HITZROT, J. M., and BOLLING, R. W.
Fractures of the neck of the scapula.—*Ann. Surg.*, 1916, lxiii, 215.

HOCH, A.
The problem of syphilitic psychoses.—*J. Nerv. & Ment. Dis.*, 1916, xiv, 170.
The dementia of the cerebral arteriosclerosis.—*Psychiat. Bull.*, 1916, ix, 306.

HOLMES, J. B.
Recent advances in anatomy, physiology, and pathology of childhood.—*Am. J. Dis. Child.*, 1916, xi, 62.
Congenital obliteration of the bile ducts: diagnosis and suggestions for treatment.—*Ibid.*, 1916, xi, 405.
The reliability of the electrical diagnosis of tetany: with especial consideration of the electrical values found in normal children.—*Ibid.*, 1916, xii, 1.
Multiple abscesses of the brain in infancy.—*Arch. Int. Med.*, 1916, xvii, 591.
Congenital obliteration of the bile-ducts.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 75.
Multiple abscesses of the brain in infancy.—*Ibid.*, 1916, xviii, 78.

HOOKER, D. R.
The influence of age upon the venous blood pressure in man.—*Am. J. Physiol.*, 1916, xl, 43.
Social hygiene—another great social movement.—*Soc. Hyg.*, 1916, ii, 5.

HOPKINS, J. G., and ZINSSER, H.
On a species of Treponema found in rabbits.—*J. Bact.*, 1916, i, 489.
Studies on Treponema pallidum and syphilis. ii. Spirochaeticidal antibodies against Treponema pallidum.—*J. Exper. M.*, 1916, xxiii, 323.
Studies on Treponema pallidum and syphilis. iii. The individual fluctuations in virulence and comparative virulence of Treponema pallidum strains passed through rabbits.—*Ibid.*, 1916, xxiii, 329.

HOPKINS, J. G., ZINSSER, H., and MCBURNEY, M.
Studies on Treponema pallidum and syphilis. iv. The difference in behavior in immune serum between cultivated non-virulent Treponema pallidum and virulent treponemata from lesions.—*J. Exper. M.*, 1916, xxiii, 341.
Studies on Treponema pallidum and syphilis. v. Further studies on the relation of culture pallida to virulent pallida and on reinfection phenomena.—*Ibid.*, 1916, xxiv, 561.

HOWARD, C. P.
The symptoms and physical signs resulting from wounds of the chest.—*Am. J. M. Sc.*, 1916, cliii, 650.

HOWELL, W. H.
Structure of the fribrin-gel and theories of gel-formation.—*Am. J. Physiol.*, 1916, xl, 526.

HOWLAND, J.
Acidosis in infancy and childhood.—*Tr. Ass. Am. Phys.*, 1916, xxxi.

HOWLAND, J., and HOLT, L. E.
Diseases of infancy and childhood.—7 ed. N. Y. & Lond., 1916, D. Appleton & Co., 1161 p. 8°.

HOWLAND, J., HAESLER, F. H., and MARRIOTT, W. McK.
The use of a new reagent for microcolorimetric analysis as applied to the determination of calcium and of inorganic phosphates in the blood serum.—*Proc. Am. Soc. Biol. Chemists*, 1916, p. xviii.

HOWLAND, J., and MARRIOTT, W. McK.
Acidosis occurring with diarrhea.—*Am. J. Dis. Child.*, 1916, xi, 309.
Acetone body production in infancy and childhood.—*Ibid.*, 1916, xii, 459.
Phosphate retention as a factor in the production of acidosis in nephritis.—*Arch. Int. Med.*, 1916, xviii, 708.; also *Tr. Am. Soc. Adv. Clin. Investigation*, 1916, viii.
A discussion of acidosis, with special reference to that occurring in the diseases of childhood.—*Arch. Pediat.*, 1916, xxxiii, 124; also *Am. J. Obst.*, 1916, lxxiii, 556; *Med. Rec.*, 1916, lxxxix, 125.
The calcium content of the blood in rickets and tetany.—*Tr. Am. Pediat. Soc.*, 1916, xxviii.

HUNNER, G. L.
Stricture of the ureter. Excluding tuberculosis and calculus: report of 50 cases.—*N. York M. J.* [etc.], 1916, civ, 5.
Treatment of ureteral stricture with special reference to retrograde dilatation.—*South. M. J.*, 1916, ix, 616.

HURD, H. M.
Some sources of friction in the management of hospitals.—*Mod. Hosp.*, 1916, vi, 30.
Another source of friction in hospital administration.—*Ibid.*, 1916, vi, 112.
Who shall manage the training school for nurses?—*Ibid.*, 1916, vi, 114.
Advantages of the budget system.—*Ibid.*, 1916, vi, 186.
Nathan Smith, Nathan R. Smith, and Alan P. Smith—a medical family.—*Maryland M. J.*, 1916, lix, 56; also *Bull. Med. & Chir. Fac. Maryland*, 1915-16, viii, 157.
Need of segregation of imbecile women.—*Maryland Psychiat. Q.*, 1915-16, v, 64.

HURD, H. M. [and others].
The institutional care of the insane in the United States and Canada. 2 v. Balt., 1916, Johns Hopkins Press. 497; 897 p. 8°.

HURWITZ, S. H.
Preliminary tests of the blood in transfusions.—*Calif. State J. M.*, 1916, xiv, 318.

HURWITZ, S. H., and LUCAS, W. P.
A study of the blood in hemophilia.—*Arch. Int. Med.*, 1916, xvii, 543.

HURWITZ, S. H., and MEYER, K. F.
Studies on the blood proteins. I. The serum globulins in bacterial infection and immunity.—*J. Exper. M.*, 1916, xxiv, 515.

HURWITZ, S. H., and TRANTER, C. L.
On the reaction of the cerebrospinal fluid.—*Arch. Int. Med.*, 1916, xvii, 828.

HUTCHINS, H. T.
The rôle of the anteposed uterus in the causation of backache and pelvic symptoms.—*J. Am. M. Ass.*, 1916, lxvii, 940.

INGRAHAM, C. B.
The etiology and diagnosis of endometritis.—*Colorado Med.*, 1916, xiii, 19.

JANEWAY, T. C.
Management of patients with chronic renal disease.—*Am. J. M. Sc.*, 1916, cli, 137; also *Bull. Med. & Chir. Fac. Maryland*, 1915-16, viii, 103.
The etiology of the diseases of the circulatory system. (Shattuck lecture.)—*Boston M. & S. J.*, 1916, clxxiv, 915.

JELKS, E., and PEYTON, H. A.
Pyelography as an aid to the diagnosis of certain obscure renal and abdominal conditions.—*J. Florida M. Ass.*, 1916, iii, 129.

JONES, W.
Presidential address. An indirect method of determining pyrimidine groups in nucleotides.—[Abstr.] *Proc. Am. Soc. Biol. Chemists*, 1916, p. x.
The admissibility of ammonium magnesium phosphate as a form in which to weigh phosphoric acid.—*J. Biol. Chem.*, 1916, xxv, 87.

JONES, W., and GERMANN, H. C.
Hydrolysis of yeast nucleic acid with ammonia.—*J. Biol. Chem.*, 1916, xxv, 95.

KEITH, N. M., and LAMSON, P. D.
The rôle of the liver in acute polycythemia. III. The relation of plasma volume to the number of erythrocytes per unit volume of blood.—*J. Pharmacol. & Exper. Therap.*, 1916, viii, 247.

KELLY, H. A.
Some radium achievements.—*Am. J. Surg.*, 1916, xxx, 73.
Double shame of Baltimore. Her unpublished vice report, her indifference.—*Delaware State M. J.*, 1916, vii, 2.
Radium therapy in cancer of the uterus.—*Tr. Am. Gynec. Soc.*, 1916, xli, 532.
Radiotherapy.—*Tr. M. Ass. Alabama*, 1916.
Radium and lymphosarcoma.—*Tr. South. Surg. & Gynec. Ass.*, 1916, xxix.
Treatment of fibroid tumors with radium.—*Woman's M. J.*, 1916, xxvi.

KELLY, H. A., and BURNAM, C. F.
A résumé of results in the radium treatment of 347 cases of cancer of the uterus and vagina.—*Am. J. Obst.*, 1916, lxxiv, 326.
Radium in the treatment of carcinomas of the cervix uteri and vagina.—*Radium*, 1916, vi, 73; also *Tr. Am. Gynec. Soc.*, 1916, xli.
Treatment of lymphosarcoma with radium.—*Tr. South. Surg. & Gynec. Ass.*, 1916, xxix.

KELLY, H. A., and NEILL, W.
Cauterization and fulguration of bladder tumors.—*J. Am. M. Ass.*, 1916, lxvi, 721.

KEMPF, E. J.
Two methods of subjective learning in the monkey, Macacus rhesus.—*J. Animal Behavior*, 1916, vi, 256.
Did consciousness of self play a part in the behavior of this monkey?—*J. Philos. Psychol.* [etc.], 1916, xiii, 410.

KETRON, L. W., and GILCHRIST, T. C.
Report of two cases of idiopathic hemorrhagic sarcoma (Kaposi), one presenting unusual features, with special methods of treatment and investigation.—*J. Cutan. Dis. incl. Syph.*, 1916, xxxiv, 429.
A unique case of atrophy of the fatty layer of the skin, preceded by the ingestion of the fat by large phagocytic cells—macrophages.—*Ibid.*, 1916, xxxiv, 728.

KETRON, L. W., and KING, J. H.
Gastro-intestinal findings in acne vulgaris, especially fluoroscopic.—*J. Am. M. Ass.*, 1916, lxvii, 671.

KING, J. H.
The effect of removal of the spleen upon the metabolism in dogs. Preliminary report.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 7.

KING, J. H., BERNHEIM, B. M., and JONES, A. T.
The effect of removal of the spleen upon blood transfustion.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 10.

KING, J. H., and KETRON, L. W.
Gastro-intestinal findings in acne vulgaris, especially fluoroscopic.—*J. Am. M. Ass.*, 1916, lxvii, 671.

KING, J. T., JR.
The quantitative effect of salvarsan on the Wassermann reaction of the blood.—*J. Am. M. Ass.*, 1916, lxvii, 1669.

KNOX, J. H. M.
A case of acute myelogenous leukemia in an infant.—*Am. J. Dis. Child.*, 1916, xi, 462.
The diet of children after infancy.—*J. Am. M. Ass.*, 1916, lxxvii, 432.
Infant welfare work; its necessity—its reward.—*Maryland M. J.*, 1916, lix, 170; also *Pediatrics*, 1916, xxviii, 490.
Report of a case of myelogenous leukemia in an infant nine months old.—*Pediatrics*, 1916, xxviii, 74.

KNOX, J. H. M., WAHL, H. R., and SCHMEISSER, H. C.
Gaucher's disease. A report of two cases in infancy.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 64.

KRAUSE, A. K.
Attempts to alter the resistance of guinea pigs to tuberculous infection and extension by anaphylactic shock.—*Nat. Ass. Study & Prev. Tubere. Tr.*, 1916, xii, 231.
Experimental studies on cutaneous hypersensitiveness to tuberculoprotein.—*Ibid.*, 1916, xii, 233.
Some unusual consequences of artificial pneumothorax.—*Ibid.*, 1916, xii, 234.
Cellular or tissue immunity to tuberculosis and its relation to the pathology of tuberculosis.—*Ibid.*, 1916, xii, 243.
Studies in immunity to tuberculosis. Experimental studies on the cutaneous reaction to tuberculo-protein. First paper. Factors governing the reaction.—*J. Med. Research*, 1916, xxxv, 1.
Studies in immunity to tuberculosis. The anaphylactic state in its relation to resistance to tuberculous infection and tuberculous disease. An experimental study.—*Ibid.*, 1916, xxxv, 25.
Studies in immunity to tuberculosis. Concerning the general tuberculin reaction.—*Ibid.*, 1916, xxxv, 43.
How we can help the tuberculous.—*J. Outdoor Life*, 1916, xiii, 372.
Edward L. Trudeau: a study.—*Med. Pickwick*, 1916, ii, 83.

LANDOIS, F., and BURCKHARDT, H.
Erfahrungen über die Behandlung inficierter Gelenke im Kriege.—*Beitr. z. klin. Chir.*, 1916, xcviii, 358.

LAWLER, ELSIE M.
How much time should be allowed for specialization during the training school course?—*Johns Hopkins Nurses Alumnæ Mag.*, 1916, xv, 248; also *Am. J. Nursing*, 1916, xvi, 839.

LEONARD, V. N., and DAYTON, A. B.
Multiple acute gastric ulcers after using Percy's "Cold iron" for inoperable carcinoma; preliminary report of a fatal case.—*J. Am. M. Ass.*, 1916, lxvi, 1549.

LEVY, R. L.
Conditions of activity in endocrine glands. Effect of thyroid secretion on pressor action of epinephrin.—*Am. J. Physiol.*, 1916, xli, 492.

LEVY, R. L., and ROWNTREE, L. G.
On the toxicity of various commercial preparations of emetin hydrochlorid.—*Arch. Int. Med.*, 1916, xvii, 420.
A study of the buffer value of the blood.—*Ibid.*, 1916, xvii, 525.

LEWIS, D. S., and MOSENTHAL, H. O.
A comparative study of tests for renal function: Phenolsulphonephthalein, nonprotein nitrogen and urea nitrogen of the blood, Ambard's coefficient of urea excretion and the test meal for renal function.—*J. Am. M. Ass.*, 1916, lxvii, 933.

LISSER, H.
The eye, ear, nose and throat in disease of the thyroid and thymus.—*Ophth. Rec.*, 1916, xxv, 433.

LYMAN, D. R.
The development of the tuberculosis crusade and its needs.—*Lancet-Clinic*, 1916, cxvi, 193.
A case of unsuspected spontaneous pneumothorax.—*Tr. Am. Climat. Ass.*, 1916, xxxii.

MACCALLUM, W. G.
A text-book of pathology. Phila., 1916, W. B. Saunders Co. 1100 p. 8°.

MCCLURE, R. D.
Pernicious anemia treated by splenectomy and systematic, often-repeated transfusion of blood; transfusion in benzol poisoning.—*J. Am. M. Ass.*, 1916, lxvii, 793.

MCCLURE, W. B., HOFFMAN, W. H., and SAUER, L. W.
Simultaneous injections of streptococci and dahlia in the guinea-pig.—*J. Infect. Dis.*, 1916, xviii, 353.

MCCRAE, T.
An epidemic of pneumococcus infection.—*Canad. M. Ass. J.*, 1916, vi, 769.
Chronic arthritis.—*Penn. M. J.*, 1916, xix, 501.
The separation of tuberculosis from general medicine.—*Nat. Ass. Study & Prev. Tubere. Tr.*, 1916, xii, 83.

MCCRAE, T., and COPLIN, W. M. L.
Gelatinoid carcinoma (morbus gelatinosus) of the peritoneum.—*Am. J. M. Sc.*, 1916, cli, 475.

MCCRAE, T., and FUNK, E. H.
Bronchiectasis of the upper lobes, with report of five cases with necropsies.—*J. Am. M. Ass.*, 1916, lxvii, 1060.

MACKENZIE, J. N.
Some reminiscences, reflections and confessions of a laryngologist.—*J. Laryngol.*, 1916, xxxi, 411; also *Ann. Otol., Rhinol. & Laryngol.*, 1916, xxv, 61.

MAJOR, R. H.
The work at Rosedale. [University of Kansas School of Medicine.]—*Kansas M. J.*, 1916, xvi, 106.

MALL, F. P.
On the study of racial embryology.—Johns Hopkins Univ., Dept. Embryology, 1916. Pamphlet. (Privately printed.)
The human magna reticulé in normal and in pathological development.—Wash., 1916, Carnegie Inst., Wash., Publ. No. 224.
On several anatomical characters of the human brain said to vary according to race and sex, with especial reference to the weight of the frontal lobe.—*Atlanta Univ. Publ.*, 1916, No. 20.

MARRIOTT, W. McK.
Progress in pediatrics: review of the literature on the metabolism of normal infants.—*Am. J. Dis. Child.*, 1916, xii, 88.
A method for the determination of the alkali reserve of the blood plasma.—*Arch. Int. Med.*, 1916, xvii, 840.
The therapeutic value of the hypophosphites.—*J. Am. M. Ass.*, 1916, lxvi, 486.
The determination of alveolar carbon dioxid tension by a simple method.—*Ibid.*, 1916, lxvi, 1594.
A simplified procedure for the determination of the carbon dioxide tension in the alveolar air.—*Proc. Am. Soc. Biol. Chemists*, 1916, p. xviii.

MARRIOTT, W. McK., and HOWLAND, J.
Acidosis occurring with diarrhea.—*Am. J. Dis. Chil.*, 1916, xi, 309.
Acetone body production in infancy and childhood.—*Ibid.*, 1916, xii, 459.
Phosphate retention as a factor in the production of acidosis in nephritis.—*Arch. Int. Med.*, 1916, xviii, 708; also *Tr. Am. Soc. Adv. Clin. Investigation*, 1916, viii.
A discussion of acidosis, with special reference to that occurring in the diseases of childhood.—*Arch. Pediat.*, 1916, xxxiii, 124; also *Am. J. Obst.*, 1916, lxxiii, 556; *Med. Rec.*, 1916, lxxxix, 125.
The calcium content of the blood in rickets and tetany.—*Tr. Am. Pediat. Soc.*, 1916, xxviii.

MARRIOTT, W. McK., HOWLAND, J., and HAESLER, F. H.
The use of a new reagent for microcolorimetric analysis as applied to the determination of calcium and of inorganic phosphates in the blood serum.—*Proc. Am. Soc. Biol. Chemists*, 1916, p. xviii.

MARSHALL, H. T.
Osteoma.—*Ref. Handb. Med. Sc., N. Y.* 3d ed. 1916, vi, 925.

MARSHALL, H. W.
A case of multiple cartilaginous exostoses.—*Am. J. Orthop. Surg.*, 1916, xiv, 346.
Chronic backache.—*Boston M. & S. J.*, 1916, clxxiv, 591.

MEYER, A.
The scope of psychopathology.—*Psychiat. Bull.*, 1916, ix, 297.
The extra-institutional responsibilities of state hospitals for mental diseases.—*Proc. Joint Board Trustees, State Hosp. Mich.*, 1916, 5.
Mental diseases, pathology.—*Ref. Handb. Med. Sc., N. Y.*, 3d. ed., 1916, vi, 400.
The right to marry. What can a democratic civilization do about heredity and child welfare?—*Survey*, 1916, xxxvi, 243.

MILLER, G. B.
Etiology of sterility in women.—*Am. J. Obst.*, 1916, lxxiv, 450.

MILLER, R. T.
Acute suppurative pancreatitis. Gangrene of the major portion of the pancreas. Recovery. Determination of pancreatic function three years subsequently.—*Ann. Surg.*, 1916, lxiv, 320.
Retroperitoneal rupture of the duodenum by blunt force.—*Ann. Surg.*, 1916, clxi, 48.
The surgical treatment of ascites. Direct drainage of the fluid into the blood stream by implantation of the saphenous vein in the peritoneum; report of five cases.—*Penn. M. J.*, 1915-16, xix, 413.

MILLER, S. R., BAETJER, W. A., and BARKER, L. F.
The clinical diagnosis of acute leukemic states.—*South. M. J.*, 1916, ix, 107.

MINOT, G. R.
Studies on a case of idiopathic purpura hemorrhagica.—*Am. J. M. Sc.*, 1916, clxi, 48.
Methods for testing donors for transfusion of blood and consideration of factors influencing agglutination and hemolysis.—*Boston M. & S. J.*, 1916, clxxiv, 667.
The effect of temperature upon the clotting time (prothrombin time) of oxalated plasma with calcium.—*J. Med. Research*, 1915-16, xxxiii, 503.

MINOT, G. R., and DENNY, G. P.
The coagulation of blood in the pleural cavity.—*Am. J. Physiol.*, 1915-16, xxxix, 455.

MINOT, G. R., DENNY, G. P., and DAVIS, D.
Prothrombin and antithrombin factors in the coagulation of blood.—*Arch. Int. Med.*, 1916, xvii, 101.

MINOT, G. R., and LEE, R. I.
The blood platelets in hemophilia.—*Arch. Int. Med.*, 1916, xviii, 474.

MINOT, G. R., LEE, R. I., and VINCENT, B.
Splenectomy in pernicious anemia; studies on bone marrow stimulation.—*J. Am. M. Ass.*, 1916, lxvii, 719.

MINOT, G. R., and SELLARDS, A. W.
The antagonistic action of negative sera upon the Wassermann reaction.—*J. Med. Research*, 1916, xxxiv, 131.
Injection of hemoglobin in man and its relation to blood destruction, with especial reference to the anemias.—*Ibid.*, 1916, xxxiv, 469.

MORRIS, R. S.
The glucose content of the blood.—(Editorial.) *J. Lab. & Clin. M.*, 1916, i, 208.
Laboratory methods. Methods for the determination of glucose in the blood.—*Ibid.*, 1916, i, 252.
The uric acid of the blood.—*Ibid.*, 1916, i, 454.
The presence of eosinophile cells in pleural exudates.—*Ibid.*, 1916, i, 540.
Recent studies on hemophilia.—*Ibid.*, 1916, i, 714.
Tonsillectomy during the course of acute rheumatic fever.—*Ibid.*, 1916, ii, 168.

MORRIS, R. S., and WOOLLEY, P. G.
The clinic and autopsy room.—*Lancet-Clinic*, 1916, cxvi, 66, 89, 164, 233, 258, 398, 401, 404, 475, 522.

MORRISS, W. H.
Secondary hemorrhage in military surgery.—*Mil. Surgeon*, 1916, xxxviii, 131.

MOSENTHAL, H. O.
The treatment of diabetes mellitus.—*J. Med. Soc. N. Jersey*, 1916, xiii, 339.

MOSENTHAL, H. O., and LEWIS, D. S.
A comparative study of tests for renal function; phenolsulphonephthalein, nonprotein nitrogen and urea nitrogen of the blood, Ambard's coefficient of urea excretion, and the test meal for renal function.—*J. Am. M. Ass.*, 1916, lxvii, 933.

MOSENTHAL, H. O., and RICHARDS, A. E.
The interpretation of a positive nitrogen balance in nephritis.—*Arch. Int. Med.*, 1916, xvii, 329.

NAFFZIGER, H. C.
Prospects of surgical treatment in meningitis.—*Calif. State J. M.*, 1916, xiv, 322.
Certain eye and ear affections in association with head injuries.—*Ophth. Rec.*, 1916, xxv, 502.

NEEL, J. C.
Retrodisplacements of the uterus; with especial reference to their causation and a new method of treatment.—*Calif. State J. M.*, 1916, xiv, 372.
Retrodisplacements of the uterus.—*Surg. Gynec. & Obst.*, 1916, xxii, 233.

NIXON, P. I.
Chaparro amargosa in the treatment of amebic dysentery.—*J. Am. M. Ass.*, 1916, lxvi, 946.
The intravenous use of mercuric chlorid. A note on a new method of administration; with special reference to prevention of vein obliteration.—*J. Am. M. Ass.*, 1916, lxvi, 1622.
Can we diagnose appendicitis?—*Med. Rec.*, 1916, lxxxix, 469.

NUTTING, M. A.
A sounder economic basis for training schools for nurses.—*Am. J. Nursing*, 1916, xvi, 310.
Education of nurses for the home and the community.—*Mod. Hosp.*, 1916, vi, 196.

OSLER, SIR W.
Science and war; an address delivered at University of Leeds Medical School.—N. Y., 1916, Oxford Univ. 39 p. 8°.
The tuberculous soldier.—*Lancet*, 1916, ii, 220.
Local tetanus.—(Correspondence.) *Ibid.*, 1916, ii, 877.
[Remarks.] General news.—*Mil. Surgeon*, 1916, xxxix, 232.
Treatment of cerebro-spinal meningitis.—*Practitioner*, 1916, xcvi, 1.
Discussion on paratyphoid fever.—*Proc. Roy. Soc. Med.*, Lond., 1915-16, ix, Med. Sect., 38.
Discussion on trench nephritis.—*Ibid.*, Lond., 1915-16, ix, Med. Sect., xiv.

OSLER, SIR W., ROBB, A. G. [*et al.*]
Discussion on the treatment of cerebrospinal meningitis.—*Proc. Roy. Soc. Med.*, Lond., 1915-16, ix, Therap. & Pharmacol. Sect., 1.

PARFITT, C. D.
The adjustment of pressure in induced pneumothorax. With special regard to the mobility of the mediastinum as indicated by the manometer.—*Arch. Int. Med.*, 1916, xvii, 646.
Tuberculosis often of secondary importance to other pathological conditions.—*Nat. Ass. Study & Prev. Tubere. Tr.*, 1916, xii, 118.

PARK, E. A.
Review of the literature of the past two years on the organs of internal secretion.—*Am. J. Dis. Child.*, 1916, xii, 477.

PEABODY, F. W.
Some aspects of the clinical study of the respiration: the significance of alveolar air analysis.—*Am. J. M. Sc.*, 1916, cli, 184.
Tests of renal function from the standpoint of the general practitioner.—*Boston M. & S. J.*, 1916, clxxv, 158.
Some factors in the production of cardiac dyspnea.—*J. Am. M. Ass.*, 1916, lxvii, 1136.

PEABODY, F. W., HIGGINS, H. L., and FITZ, R.
Study of acidosis in three normal subjects, with incidental observations on the action of alcohol as an antiketogenic agent.—*J. Med. Research*, 1916, xxxiv, 263.

PEABODY, F. W., MEYER, A. L., and DUBOIS, E. F.
Clinical calorimetry. xvi. The basal metabolism of patients with cardiac and renal disease.—*Arch. Int. Med.*, 1916, xvii, 980.

PEARCE, LOUISE.
Klossiella infection of the guinea-pig.—*J. Exper. M.*, 1916, xxiii, 431; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 189.

PEARCE, LOUISE, and BROWN, W. H.
Chemopathological studies with compounds of arsenic. I. Types of the arsenic kidney.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1916, xxiv, 75.
Chemopathological studies with compounds of arsenic. II. Histological changes in arsenic kidneys.—*Ibid.*, 1916, xxiv, 83.
Chemopathological studies with compounds of arsenic. III. On the pathological action of arsenicals on the adrenals.—*Ibid.*, 1916, xxiv, 93.
Chemopathological studies with compounds of arsenic. IV. The character and distribution of renal injury produced by arsenicals as indicated by the processes of repair.—*J. Exper. M.*, 1916, xxiii, 443; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 189.

PENROSE, C. A.
The three phases of life.—*Maryland M. J.*, 1916, lix, 37.

PLAGGEMEYER, H. W.
Tuberculosis of the seminal duct.—*J. Mich. M. Soc.*, 1916, xv, 118.
Tuberculosis of the seminal vesicle and epididymis.—*Urol. & Cutan. Rev.*, 1916, xx, 134.

PLASS, E. D.
A fatal case of multiple primary carcinomata.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 66.
Fetal and placental syphilis.—*Am. J. Obst.*, 1916, lxxiv, 561; also *Tr. Am. Gynec. Soc.*, 1916, xli, 348.

RANDALL, A.
The relation of bladder tumors to the cancer problem.—*Therap. Gaz.* [etc.], 1916, 3. s. xxxii, 242.

RANDOLPH, R. L.
A case of blepharochalasis, a variety of dermatolysis.—*Ophth. Rec.*, 1916, xxv, 616; also *Tr. Am. Ophth. Soc.*, 1916, xiv, 518.
A case of congenital suppurative choroiditis with microphthalmos. *Ophth. Rec.*, 1916, xxv, 619.

RANDOLPH, R. L., and SCHMEISSER, H. C.
A clinical and pathological study of two cases of miliary tubercles of the choroid.—*Tr. Am. Ophth. Soc.*, 1916, xiv, 585.

REID, M. R.
Partial occlusion of the aorta with the metallic band. Observations on blood pressures and changes in the arterial walls.—*J. Exper. M.*, 1916, xxiv, 287; also *Tr. Am. Surg. Ass.*, 1916, xxxiv, 289.

REMSEN, C. M.
Suggested operative steps dealing with spontaneous intracerebral hemorrhage (apoplexy).—*Ann. Surg.*, 1916, lxiii, 513.
The relation of the pathological basis of hydrocephalus to its surgical alleviation.—*Interstate M. J.*, 1916, xxiii, 89.
The acute typhoid abdomen; with especial reference to surgical complications.—*J. Am. M. Ass.*, 1916, lxvi, 28.

REMSEN, C. M., and CRENSHAW, H.
A case of hemiparesis, ataxia and astereognosis associated with arachnoidal edema.—*J. Am. M. Ass.*, 1916, lxvi, 262.

RIGGS, T. F.
End-to-end suture of the bile-ducts.—*Surg., Gynec. & Obst.*, 1916, xxii, 660.

ROUS, P.
The influence of dieting upon the course of cancer.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1916, xxiii, 7.

ROUS, P., and JONES, F. S.
A method for obtaining suspensions of living cells from the fixed tissues, and for the plating out of individual cells.—*J. Exper. M.*, 1916, xxiii, 549; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 219.
The protection of pathogenic micro-organisms by living tissue cells.—*Ibid.*, 1916, xxiii, 601; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 227.

ROUS, P., and TURNER, J. R.
The preservation of living red blood cells *in vitro*. I. Methods of preservation.—*J. Exper. M.*, 1916, xxiii, 219; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 107.
The preservation of living red blood cells *in vitro*. II. The transfusion of kept cells.—*Ibid.*, 1916, xxiii, 239; also *Stud. Rockefeller Inst. M. Research*, 1916, xxv, 127.

ROWNTREE, L. G.
Investigations in diagnosis and treatment of acidosis.—*Tr. Ass. Am. Phys.*, 1916, xxxi.

ROWNTREE, L. G., and LEVY, R. L.
On the toxicity of various commercial preparations of emetin hydrochlorid.—*Arch. Int. Med.*, 1916, xvii, 420.
A study of the buffer value of the blood.—*Ibid.*, 1916, xvii, 525.

ROWNTREE, L. G., and MACHT, D. I.
The standardization of digitalis and the potency of American-grown digitalis.—*J. Am. M. Ass.*, 1916, lxvi, 870.

RUSHMORE, S.
Progress in gynecology.—*Boston M. & S. J.*, 1916, clxxiv, 277; 320.
Ibid., 1916, clxxv, 494.
Treatment of weak labor pains.—*Ibid.*, 1916, clxxv, 659.

SABIN, FLORENCE R.
The origin and development of the lymphatic system.—*Johns Hopkins Hosp. Rep.*, 1916, xvii, 347.
The method of growth of the lymphatic system.—*Science*, 1916, n. s., xliv, 145; also *N. York M. J.* [etc.], 1916, cili, 25.

SAMPSON, J. A.
The variations in the blood supply of the ovary and their possible operative importance.—*Tr. Am. Gynec. Soc.*, 1916, xli, 429.

SELLARDS, A. W.
Bacterial cultures of human spleens removed by surgical operation.—*J. Immunol.*, 1916, i, 321; also *N. Orl. M. & S. J.*, 1916-17, lxix, 502.

SELLARDS, A. W., and MINOT, G. R.
The antagonistic action of negative sera upon the Wassermann reaction.—*J. Med. Research*, 1916, xxxiv, 131.
Injection of hemoglobin in man and its relation to blood destruction, with especial reference to the anemias.—*Ibid.*, 1916, xxxiv, 469.

SELLING, L.
Benzol as a leucotoxin. Studies on the degeneration and regeneration of the blood and hæmatopoietic organs.—*Johns Hopkins Hosp. Rep.*, 1916, xvii, 83.

SHALLENBERGER, W. F.
Chronic urethritis in women; a new method of diagnosis in obscure urethral pain.—*J. Am. M. Ass.*, 1916, lxvi, 1011.
Some phases of nephroptosis in women.—*J. Med. Ass. Georgia*, 1915-16, v, 212.

SHARPE, W.
The cranial deformity of oxycephaly; its operative treatment, with a report of cases.—*Am. J. M. Sc.*, 1916, cli, 840.
The operative treatment of brachial plexus paralysis.—*J. Am. M. Ass.*, 1916, xlvi, 876.
Observations in the diagnosis and treatment of brain injuries in adults.—*Ibid.*, 1916, lxvi, 1536.
The results of cranial decompression in selected types of cerebral spastic paralysis due to hemorrhage.—*N. Y. State J. M.*, 1916, xvi, 475.
The operation of cranial decompression for certain intracranial conditions.—*Wisconsin M. J.*, 1916, xv, 174.

SLADEN, F. J., and WINTERNITZ, M. C.
Venous thrombosis during myocardial insufficiency.—*Johns Hopkins Hosp. Rep.*, 1916, xvii, 511.

SLEMONS, J. M.
The results of a routine study of the placenta.—*Am. J. Obst.*, 1916, lxxiv, 204.
How closely do the Wassermann reaction and the placental histology agree in the diagnosis of syphilis?—*Tr. Am. Gynec. Soc.*, 1916, xli, 363.

SLOAN, M. F.
The application of artificial pneumothorax in the treatment of pulmonary tuberculosis.—*South. M. J.*, 1916, ix, 689.

SMITH, F. J., and BARKER, L. F.,
Functional renal tests (phenolsulphonephthalein; lactose) in orthostatic albuminuria.—*Am. J. M. Sc.*, 1916, cii, 44.

SMITH, W. H.
The educational function of the hospital.—*Mod. Hosp.*, 1916, vi, 1; also *Am. J. Nursing*, 1916, xvi, 574; *Johns Hopkins N. Alumnæ Mag.*, 1916, xv, 66.
A shortsighted policy on the part of hospital trustees and hospital superintendents.—*Mod. Hosp.*, 1916 vi, 268.
President's address. The American Hospital Association. *Ibid.*, 1916, vii, 312.
Hospital policy in America. Problems of the future.—*Hospital*, Lond., 1916, lxi, 63.
What is meant by hospital efficiency and some of the factors which are responsible for lack of efficiency.—*Med. Rec.*, 1916, lxxxix, 874; also *Trained Nurse*, 1916, lvii, No. 1.

STEARNS, T., WILSON, D. W., JANNEY, J. H., JR., and THURLOW, M. DEG.
Studies on parathyroid tetany.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 12.

STEVENS, A. R.
A study of exstrophy of the bladder; with report of a case five years after implantation of the ureters into the rectum.—*Surg., Gynec. & Obst.*, 1916, xxiii, 702.

STRONG, R. P.
The plague of man.—*Lowell Lectures*, 1916.

STROUSE, S.
Prognosis and treatment of diabetes as influenced by recent studies.—*Illinois M. J.*, 1916, xxx, 332.
Diabetes and surgery; diabetes and pregnancy. The treatment of diabetic acidosis.—*Med. Clin.*, Chicago, 1916-17, ii, 37.
Diabetes in the young.—*Ibid.*, Chicago, 1916-17, ii, 327.
A case of renal glycosuria.—*Ibid.*, Chicago, 1916-17, ii, 339.

STROUSE, S., and FRANK, I.
The tuberculosis situation in Chicago as met by the Jewish charities.—*Associated Bull.*, Chicago, 1916 (Feb.).
Pollen extracts and vaccines in hay-fever.—*J. Am. M. Ass.*, 1916, lxvi, 712.

THAYER, W. S.
Adams-Stokes syndrome. Persistent bradycardia involving both auricles and ventricles. Remarkable prolongation of the As-Vs interval.—*Arch. Int. Med.*, 1916, xvii, 13.
Teaching and practice.—*Science*, 1916, n. s. xliii, 691; also *South. M. J.*, 1916, ix, 955; 1035.
Observations on the teaching of tuberculosis.—*Nat. Ass. Study & Prev. Tuberc. Tr.*, 1916, xii, 92.

THEOBALD, S.
Herpes corneæ "febrilis"; with special reference to etiology.—*N. York M. J.*, [etc.], 1916, civ, 247; also *Tr. Am. Ophth. Soc.*, 1916, xiv, 520.

TINKER, M. B.
What stomach symptoms justify surgical intervention.—*Delaware State M. J.*, 1916, vii, 3.

VANDERHOOF, D.
The significance of the tongue in the diagnosis of diseases of the stomach.—*Arch. Diag.*, 1916, ix, 23.
The consideration of the appetite.—*Internat. Clin.*, 1916, 26, s., ii, 22.
The fractional method of gastric analysis.—*South. M. J.*, 1916, ix, 683.

WARFIELD, L. M.
Note on an auscultatory sign over the manubrium.—*J. Am. M. Ass.*, 1916, lxvii, 1301.

WARFIELD, L. M., and KRISTJANSON, H. T.
An unusual case of so-called pseudoleukemia (Lymphosarcoma).—*Am. J. M. Sc.*, 1916, cli, 222.

WEED, L. H.
The establishment of the circulation of cerebro-spinal fluid.—[Abstr.] *Anat. Rec.*, 1916, x, 256.

WELCH, W. H.
Address to the graduating class, Johns Hopkins Hospital Training School for Nurses, Wednesday, May 24, 1916.—*Johns Hopkins N. Alumnæ Mag.*, 1916, xv, 140.
Medical education in the United States.—[Abstr.] *N. York M. J.* [etc.], 1916, cili, 890.
The school of hygiene and public health at the Johns Hopkins University.—*Science*, 1916, n. s., xliv, 302.

WHIPPLE, G. H.
Proteose intoxication; intestinal obstruction, peritonitis and acute pancreatitis.—*J. Am. M. Ass.*, 1916, lxvii, 15.

WHIPPLE, G. H., COOKE, J. V., and RODENBAUGH, F. H.
Intestinal obstruction. vi. A study of non-coagulable nitrogen of the blood.—*J. Exper. M.*, 1916, xxiii, 717.

WHIPPLE, G. H., and HOOPER, C. W.
Bile pigment metabolism. i. Bile pigment output and diet studies.—*Am. J. Physiol.*, 1916, xl, 332.
Bile pigment metabolism. ii. Bile pigment output influenced by diet.—*Ibid.*, 1916, xl, 349.
Icterus. A rapid change of hemoglobin to bile pigment in the pleural and peritoneal cavities.—*J. Exper. M.*, 1916, xxiii, 137.

WHIPPLE, G. H., RODENBAUGH, F. H., and KILGORE, A. R.
Intestinal obstruction. v. Proteose intoxication.—*J. Exper. M.*, 1916, xxiii, 123.

WILLIAMS, J. W.
Dispensary abuse and certain problems of medical practice.—*J. Am. M. Ass.*, 1916, lxvi, 1902; also *Bull. Med. & Chir. Fac. Maryland*, 1915-16, viii, 229.

WILSON, G.
Medical education with reference to rural communities.—*J. Am. M. Ass.*, 1916, lxvi, 1073.
Disease in apparently healthy colored girls.—*New York M. J.* [etc.], 1916, cili, 585.

WINTERNITZ, M. C.
Primary carcinoma of the liver.—*Johns Hopkins Hosp. Rep.*, 1916, xvii, 143.
Some observations on the effect of feeding glands of internal secretion to chicks.—*Ibid.*, 1916, xviii, 21.
Hyaline degeneration of the islands of Langerhans in pancreatic diabetes.—*Ibid.*, 1916, xviii, 37.
Generalized miliary tuberculosis resulting from extension of a tubercular pericarditis into the right auricle.—*Ibid.*, 1916, xviii, 49.

WINTERNITZ, M. C., and BOGGS, T. R.
Acute suppurative hypophysitis as a complication of purulent sphenoidal sinusitis.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 56.

WINTERNITZ, M. C., and SCHMEISSER, H. C.
Studies on the relation of fowl typhoid to leukemia of the fowl.—*Johns Hopkins Hosp. Rep.*, 1916, xviii, 25.

WINTERNITZ, M. C., and SLADEN, F. J.
Venous thrombosis during myocardial insufficiency.—*Johns Hopkins Hospital Rep.*, 1916, xvii, 511.

WOLMAN, S., and HAMMAN, L.
Chronic non-tuberculous pulmonary infections.—*Nat. Ass. Study & Prev. Tuberc. Tr.*, 1916, xii, 171.

WOOLLEY, P. G.
Fundamentals of pathology. For students and general practitioners of medicine and dentistry, and for nurses in training schools.—St. Louis, 1916, C. V. Mosby Co., 184 p. 8°.
Gumma of the pituitary associated with lesions in the spinal cord which may represent early lesions of syringomyelia.—*J. Lab. & Clin. M.*, 1915-16, i, 155.
Carbon dioxide and blood pressure.—(Editorial.) *Ibid.*, 1915-16, i, 203.
Nervous influence and edema.—(Editorial.) *Ibid.*, 1915-16, i, 267.
Intestinal stasis.—(Editorial.) *Ibid.*, 1915-16, i, 269.
Fetal erythroblastosis: fetal erythroblastomatosis.—*Ibid.*, 1915-16, i, 347.
The pituitary in hibernation.—(Editorial.) *Ibid.*, 1915-16, i, 456.
Heteroplastic bone and bone-marrow formation associated with tuberculosis in the adrenal.—*Ibid.*, 1915-16, i, 502.
The epiphysis (The pineal gland).—(Editorial.) *Ibid.* 1915-16, i, 527.
Cancer and X-rays.—(Editorial.) *Ibid.*, 1915-16, i, 538.
Acidosis in nephritis.—(Editorial.) *Ibid.*, 1915-16, i, 620.
Tumor problems.—(Editorial.) *Ibid.*, 1915-16, i, 625.
Diuresis.—(Editorial.) *Ibid.*, 1915-16, i, 628.
Chloroform necrosis of the liver.—(Editorial.) *Ibid.*, 1915-16, i, 630; 782.
Acidosis.—(Editorial.) *Ibid.*, 1915-16, i, 712.
The pituitary and growth.—(Editorial.) *Ibid.*, 1915-16, i, 715.
Splenectomy.—(Editorial.) *Ibid.*, 1915-16, i, 717.
Gastrointestinal diseases.—(Editorial.) *Ibid.*, 1915-16, i, 763.
The nephroses.—(Editorial.) *Ibid.*, 1915-16, i, 776.
Gastric ulcers.—(Editorial.) *Ibid.*, 1915-16, i, 928.
Edema of the lungs.—(Editorial.) *Ibid.*, 1915-16, i, 931.
The heart in pneumonia.—(Editorial.) *Ibid.*, 1915-16, i, 932.
Amyloid.—(Editorial.) *Ibid.*, 1915-16, i, 933.
Cases of infection terminating in septicemia.—*Ibid.*, 1916-17, ii, 45.
Some good autopsy figures.—*Mod. Hosp.*, 1916, vi, 377.
The autopsy room.—*Lancet-Clinic*, 1916, cxv, 313, 336, 413, 522, 564.

WOOLLEY, P. G., PEPPER, W., and BLUMER, G.
The function of the dispensary.—*J. Am. M. Ass.*, 1916, lxvi, 1156.

WOOLLEY, P. G., and MORRIS, R. S.
The clinic and autopsy room.—*Lancet-Clinic*, 1916, cxvi, 66, 89, 164, 233, 258, 398, 401, 404, 475.

YATES, J. L.
The etiology, pathology and therapy of Hodgkin's disease and allied affections.—*Colorado Med.*, 1916, xiii, 39.

YATES, J. L., and BUNTING, C. H.
Bacteriological results in chronic leukemia and pseudoleukemia.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1916, xxiv, 123.

YOUNG, H. H.
Urological examining and operating table.—*Mod. Hosp.*, 1916, vi, 457.
The Witmer form board.—*Psychol. Clin.*, 1916, x, 93.
The renaissance of urology.—*South. M. J.*, 1916, ix, 146.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

OCTOBER 16, 1916.

The first meeting of The Johns Hopkins Medical Society for the season was held on October 16, with Dr. W. S. Thayer in the chair. The following officers were elected for the ensuing year: Dr. W. W. Ford, president, and Dr. C. G. Guthrie, secretary.

1. Exhibition of Cases: Cases 1, 2 and 3. Dr. Dandy.

Case 1 (Dr. Dandy).—This is a woman who had a cerebellopontine tumor which I operated upon a month ago in Dr. Heuer's absence. She is now about ready to leave the hospital. Dr. Heuer has also two other patients, who live in the immediate vicinity and who will come before the Society to-night. Tumors were removed from both of these patients. Dr. Heuer removed one about six months ago, and the other was removed by Dr. Cushing about four years ago.

The first patient is 25 years old. Her symptoms began about one year ago with staggering gait, which gradually increased, until at the time of her admission to the hospital, she was unable to walk without support. In addition, deafness had begun in the right ear about the same time, and had also progressed, until on admission she was totally deaf on this side. She had had at times a little rigidity and tenderness in the occipital region, but nothing of any marked importance. She had also noticed a gradual diminution of vision in the left eye. A congenital cataract was present in the right eye. At times there had been attacks of amaurosis.

On admission, with the exception of a moderate grade of choked disc, there were present no signs of intracranial pressure. She had no vomiting and no headache. The symptoms suggested definitely localization in the region of the cerebellopontine angle. There was complete deafness and absence of any caloric response in the eighth nerve, with absence of bone conduction and air conduction. The Bárány test gave no response. A very slight facial weakness seemed to be present, with possibly a little weakness of the masseter muscles. There was a slight implication of the fifth and seventh nerves and a complete involvement of the eighth nerve, the syndrome of the typical endothelioma of the eighth nerve. She had most marked cerebellar signs, very marked staggering gait; in fact she could not walk alone. The Romberg test was decidedly positive. She would fall in any direction, but more to the right. She had also a very distinct nystagmus, quick to the right and slow to the left. Ataxia of the left hand was marked and there was also diadokokinesia.

The operation was done about a month ago, the usual cerebellar exploration, and an enucleable tumor was found embedded in the pons and medulla. It shelled out as a whole quite readily. She has had a perfectly uneventful recovery. Her symptoms are still marked. She has all the cerebellar symptoms and the eighth nerve involvement, but is improving very markedly day by day. She can now walk alone. The patient will, of course, continue to improve.

Case 2 (Dr. Dandy).—This patient is a man about 50 years old, on whom I did a decompression for a perfectly unlocalizable tumor about four years ago when Dr. Cushing was away. He had nothing but the symptoms of general intracranial pressure. At the operation the tumor was found, and was removed one month later by Dr. Cushing. It was a large dural endothelioma from the right temporal lobe. After this, the patient had some weakness of the left hand, which has gradually cleared up.

Case 3 (Dr. Dandy).—This man was operated upon by Dr. Heuer, who removed a large dural endothelioma from the pre-Rolandic region about six months ago. There is a marked contrast between Case 2 and Case 3. This patient, a man of 53, had no signs of intracranial pressure whatever, unless one might take a few spells of indigestion as meaning intracranial symptoms. He had absolutely no choked disc. His symptoms were a slight weakness in the left leg, which gradually involved the left arm during about one year. About a year ago when the symptoms began, he was operated upon by an outside surgeon for a deformity of the foot. This undoubtedly was due to the beginning of his pyramidal tract involvement. Looking at this patient as he walks, you can see the almost perfect result. On looking at his head, one could hardly tell he had had a cranial operation. There is only a slight depression, which is evident on looking straight at the wound. Dr. Heuer removed a good portion of the dura with the tumor, so that it could not recur. Over this defect in the dura, he placed some fascia taken from the thigh, and this has been partially responsible for the good cosmetic result. It has been six months since the operation and the patient has practically no residuum. At the time of operation, he had a very marked typical spastic hemiplegic gait, but he now shows nothing and is entirely cured.

These two cases show a very marked difference in the manifestations of intracranial tumors, both in the same region. One patient had almost entirely general and no local manifestations; the other had all local, without any general, manifestations. This is a type of tumor of which we have had a considerable number, and of which there is very little chance of recurrence. They can be permanently cured.

2. Exhibition of a Case of Gigantism in a Girl 12 Years of Age. Dr. G. J. Heuer.

K. G. Age 12, school girl. *Complaint:* Nervousness and headaches.

Family History: Both parents are living and well. The mother is rather obese but not over the normal height; the father is a tall, large man. There are eight sisters and one brother living—all apparently normal children.

Past History: The patient was born in a normal labor. Her mother states that she was a large child, weighing, she thinks, 12 pounds. She is not very clear as to the child's growth, but she thinks that the child grew faster than her other children and that her growth has been progressive and not especially rapid in the last few years. The girl herself states that she has grown rapidly in the past three years. At the age of five she had measles, and there followed a series of complications which confined her to bed for three months. There is no history of whooping-cough or diphtheria. She had chorea at the age of seven. During the attacks she was particularly bothered by twitching of the face; occasionally her whole body jerked. She was never kept out of school on account of this trouble. She has suffered from headache since the age of six, when she started to school. She has worn glasses for about six years. There has been definite shortness of breath on exertion and occasional palpitation of the heart. No edema of the extremities. No precordial pain. The appetite has been very good. The bowels have been regular. She is exceptionally fond of candy and she drinks large amounts of water. She gets up at night three or four times to void. Menstruation has not yet appeared. The breasts have just begun to enlarge. Some pubic hair has appeared in the past year.

Present Illness: The patient enters the hospital because of headaches and nervousness. The headaches began six years ago, when she first entered school. The pain begins over the left eye and radiates backward. It has been worse in the morning. The use of glasses has not improved the condition. There has never been vomiting associated with the headaches. There has been no disturbance of vision. Within the past year the girl has been

especially nervous. She cannot remain long at one occupation, has grown fidgety and restless. She has, of course, been aware of her abnormal height, but has never been troubled by it in any way. She states that she tires rather more easily on exertion than she thinks she should. She has always been slender. She is rather above the average in intelligence. At the age of 12 she is in the high school. She reads literature rather advanced for her age.

Examination: The girl is 6 feet, 1 inch in height. She weighs 117½ pounds. The skin is soft, with a tendency toward dryness rather than moisture. There is no increased wrinkling of the skin. The hair is fine. There is some fullness of the frontal bosses. The biparietal diameter of the skull is not great. The head is not long anteroposteriorly. The nose is a little wide, but not abnormally large. The jaw is not especially over-developed. The teeth meet accurately; if anything, the lower teeth fall behind the upper. The extremities are abnormally long; the hands and feet very large, but there are no acromegalic features. Examination of her cranial nerves shows no disturbances. The fundi are normal. The visual fields show a defect in the upper outer quadrant of each visual field, suggesting a beginning bitemporal hemianopsia. The neurological examination is otherwise quite negative. The X-ray of the skull shows an enlarged sella turcica, with atrophy of the posterior clinoid processes.

Thyroid: The isthmus is just palpable. Neither lobe can be definitely felt. There is no enlargement of the neck. No dullness behind the manubrium on percussion. No signs indicative of hyper- or hypothyroidism.

Adrenals: No abnormal pigmentation of the body. No pigmentation of the mucous membranes. No abdominal masses felt. There is considerable spasticity of the sigmoid.

Ovaries: A gynecological examination has not been made. On abdominal palpation nothing abnormal is made out. Menstruation has not begun.

Pineal Gland: Nothing abnormal is noted.

Laboratory Findings: Urine: There is a history of abnormal thirst. The patient rises three or four times at night to void. The average daily output of urine is 1500 cc. The average intake of water about 2000 cc. Three specimens of urine have shown a slight trace of albumin. Sugar has never been present. The specific gravity has varied between 1007 and 1013. The *chlorides* have been decreased.

Blood: Hemoglobin 71%. Polymorphonuclear neutrophiles, 61.2%; large mononuclears, 10.4%; small mononuclears, 22.4%.

Sugar Tolerance Test: One hundred grams of glucose given upon an empty stomach cause a hypoglycemia. Half an hour after the administration of 100 grams of glucose the blood sugar was the same as that of the control, that is, .95%; 1½ hours later it fell to .67%; 2 hours later to .63%.

The pharmaco-dynamic tests, *i. e.*, the responses to adrenalin and atropin, are normal.

(The pulse has been about 90. The temperature was slightly elevated on admission, but has since tended to be subnormal.)

DISCUSSION.

DR. BARKER: One interesting point about the reason why the extremities grow long might be brought out. Dr. Heuer spoke of the fact that this is the kind of gigantism which occurs before puberty. The explanation assigned is this. When the external secretion of the gonads begins at puberty, it causes the closure of the epiphyses. As long as they are not closed the long bones can grow and acromegaly does not appear. This is a most interesting example of this type.

DR. THAYER: We have had a certain number of cases of this type, have we not?

DR. HEUER: Yes, but never such a pure example.

DR. THAYER: I remember one such case we had here nearly 20 years ago at least, a most interesting case of a man who had in addition an arthritis. He had these very long, tapering fingers, was very tall and had none of the ordinary stigmata of acromegaly. We had no X-rays then for detailed examinations. The case was recorded as one of acromegaly occurring before the age of puberty.

3. Action of Opium Alkaloids on the Ducts of the Testis.

DR. DAVID I. MACHT.

Following the author's experiments on the action of drugs on the ureter, which were first announced in this journal (Bull. Johns Hopkins Hosp., 1916, XXVII, 119), attention was logically directed to the behavior of the vas deferens and seminal vesicle, which anatomically is only a diverticulum of the vas. The organs of the rabbit, guinea-pig, rat, cat, dog, sheep, and bull were utilized. The action of opium alkaloids distinguishes two groups. Those of the phenanthrene group, of which morphin and codein are the chief representatives, cause increase in tonicity and stimulation of contractions, of the vas deferens, ejaculatory duct, and seminal vesicle. Those of the isoquinoline group, of which papaverin and narcotin are the principal members, relax the tone and inhibit the contractions of the same organs. In a combination of all the opium alkaloids such as pantopon, the narcotin-papaverin effect on smooth muscle predominates. These results were, as far as possible, checked up with observations on the organs *in situ* (rabbits and guinea-pigs) and were found to hold good in the intact animal. The above observations are of some practical interest.

4. Studies on the Physiology of Thyroid Secretion (Abstract).[1]

ROBERT L. LEVY, M. D.

The recent work of Cannon and Cattell has placed the secretory innervation of the thyroid gland on a firm basis. These observers have employed as their criterion of secretory activity the electrical change giving rise to the current of action. They have demonstrated that an action current is produced in the thyroid by stimulation of the cervical sympathetic nerve or by the injection of minute amounts of the sympatheticomimetic substance, adrenin. The gland secretes promptly on stimulation, *i. e.*, an action current is obtained after a latent period of only a few seconds. No evidence of secretory activity is observed on stimulation of the vagus nerves, nor is there any electrical change after injection of the vagotropic drug, pilocarpine.

As a result of these studies, two methods are at hand for inducing secretory activity in the thyroid gland. It is the object of the present communication to present evidence of the presence of thyroid secretion in the circulating blood after stimulation of the cervical sympathetic nerves or after injection of adrenin and to demonstrate that thyroid secretion increases the effectiveness of adrenin in raising arterial pressure. Its effects on blood pressure and pulse rate are also recorded.

The results of the experiments may be summed up as follows:

1. In cats, after stimulation of the cervical sympathetic in the neck, there can be demonstrated an increase of the effectiveness of adrenin in raising arterial pressure. This increase may be as much as 200 to 300 per cent.

2. Injections of adrenin, even in minute amounts, produce a similar effect.

3. This effect is manifest only after a latent period, which may vary from about 40 to 60 minutes. There is then a progressive increase in the height of the curves, the maximum being reached

[1] These studies were carried out in the laboratory of physiology in the Harvard Medical School. It is a pleasure to acknowledge my indebtedness to Dr. W. B. Cannon for much helpful advice. The work is reported in full in the Amer. Jour. of Physiol., 1916, XLI, 492.

in from two to three hours after stimulation. The effect is of considerable duration, having been observed for as long as seven hours.

4. When the thyroid glands have been previously removed, cervical sympathetic stimulation or adrenin injection does not produce an increase in the pressor response to adrenin. It is therefore justifiable to conclude that (a) stimulation of the cervical sympathetic or adrenin injection induces secretory activity in the thyroid gland (thus confirming the observations of Cannon and Cattell); and (b) thyroid secretion renders more excitable the sympathetic structures acted on by adrenin in raising arterial pressure.

5. Stimulation of the cervical sympathetic causes the thyroid to secrete promptly, since thyroidectomy immediately after stimulation is followed by a progressive augmentation in pressor response similar to that observed when the glands are left in the animal throughout the course of the experiment.

6. Intravenous injection into thyroidectomized cats of a solution of the crystalline, iodin-containing compound isolated from the thyroid by Kendall, is followed by an increase in the efficacy of adrenin as a pressor agent. The effect is demonstrable almost immediately after injection and is of relatively shorter duration than in the stimulation experiments. This substance causes no appreciable alteration in blood pressure or pulse rate.

7. Neither during nor after stimulation of the thyroid gland through its secretory nerves is there any significant change in blood pressure or pulse rate.

8. After thyroid stimulation, even at the time when adrenin is more effective as a pressor agent, there is no increase in the augmentation of pulse rate produced by adrenin injection. This indicates a selective action of thyroid secretion in sensitizing sympathetic tissues to the action of adrenin, since the increase in vascular response is not associated with greater excitability of the augmentors of the heart.

9. In cats whose adrenal glands have been previously removed, there can be demonstrated, after thyroid stimulation, an increase in pressor response similar to that seen in unoperated animals. Though there is some evidence in the literature indicating that thyroid secretion acts as a secretory stimulant to the adrenals, the increased effectiveness of adrenin as a pressor agent after thyroid stimulation is not dependent on a greater amount of circulating adrenin.

5. Some Results of Plastic Surgery. Dr. J. S. Davis.

Dr. Davis presented a series of lantern slides, showing some of the results he had obtained in cases requiring plastic operations. Interesting pictures were shown of cases of severe burns of the hands, with subsequent loss of flexion or extension, which were restored to usefulness. Good cosmetic and functional results were shown following plastic operations and whole thickness skin grafting in cases of ectropion of the eyelids, and eversion of the lower lip. Other cases included the formation of a cheek after destruction of tissue following removal of a sarcoma; the formation of an ear to replace one lost by trauma; the filling in of the orbit with a pad of fat and skin, following enucleation of the eye with removal of the eyelids; relief of contracture of the axilla following a burn; the correction of saddle nose with a free cartilage transplant. In each instance the patient was much improved both as to function and appearance.

BOOKS RECEIVED.

A Text-Book of Pathology. By W. G. MacCallum. With 575 illustrations, chiefly from drawings by Alfred Feinberg. 1916. 8°. 1085 pages. W. B. Saunders Company, Philadelphia and London.

A Text-Book of Practical Gynecology. For Practitioners and Students. By D. Tod Gilliam, M. D., and Earl M. Gilliam, M. D. Fifth revised edition. Illustrated with 250 engravings, a colored frontispiece, and 13 full-page half-tone plates. 1916. 8°. 681 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

Practical Massage and Corrective Exercises. By Hartvig Nissen. Revised and enlarged edition of the author's "Practical Massage in Twenty Lessons"; with many additions. With 68 original illustrations, including several full-page half-tone plates. 1916. 12°. 211 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

Venesection. A Brief Summary of the Practical Value of Venesection in Disease. For Students and Practitioners of Medicine. By Walton Forest Dutton, M. D. Illustrated with several text engravings and three full-page plates, one in colors. 1916. 8°. 221 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

Christianity and Sex Problems. By Hugh Northcote, M. A. Second edition. Revised and enlarged. 1916. 8°. 478 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

The Non-Surgical Treatment of Intestinal Stasis and Constipation. Compiled by Robert H. Ferguson, M. D., Sc. D. Also an important announcement regarding liquid petrolatum. 1916. 12°. 109 pages. E. R. Squibb & Sons, New York.

Metropolitan Asylums Board. Annual report for the year 1915. (18th year of issue.) 1916. 8°. 61 pages. Printed by Henderson & Spalding, London.

The Johns Hopkins Hospital Reports. Vol. XVIII, Fasciculus 1. Annual Report of the Department of Pathology of the Johns Hopkins University and Hospital. No. 1. 1916. 4°. 102 pages. The Johns Hopkins Press, Baltimore.

The Treatment of Infantile Paralysis. By Robert W. Lovett, M. D. With 113 illustrations. 1916. 8°. 163 pages. P. Blakiston's Son & Co., Philadelphia.

Nursing Problems and Obligations. By Sara E. Parsons, R. N. 1916. 12°. 149 pages. Whitcomb & Barrows, Boston.

Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes. By Charles A. Elsberg, M. D., F. A. C. S. With 158 illustrations, three of them in colors. 1916. 4°. 330 pages. W. B. Saunders Company, Philadelphia and London.

Roentgenographic Diagnosis of Dental Infection in Systemic Diseases. By Sinclair Tousey, A. M., M.D. 1916. 8°. 75 pages. Paul B. Hoeber, New York.

The Medical Clinics of Chicago. Vol. II, No. 1, July, 1916. 1916. 8°. 220 pages. W. B. Saunders Company, Philadelphia and London.

The Treatment of Diabetes Mellitus. With Observations upon the Disease Based upon 1000 Cases. By Elliott P. Joslin, M. D. Illustrated. 1916. 8°. 440 pages. Lea & Febiger, Philadelphia and New York.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.